Sage Therapeutics®

2022 ANNUAL REPORT

Seeing the brain differently *makes a world of difference*

To our shareholders

April 2023

At Sage, we are driven to develop brain health medicines that deliver what matters most to patients. In this day and age our work is more important than ever. Brain health disorders are among the leading causes of disability worldwide and millions of people have waited decades for new treatment options that better serve the needs of patients, providers, and society. In mental health specifically, we are at a tipping point as the rates of depression continue to accelerate. In the first year of the COVID-19 pandemic, global prevalence of anxiety and depression increased by a massive 25%, according to the World Health Organization (WHO). Change is desperately needed. We are acting with a tremendous sense of urgency and challenging scientific convention to pursue breakthroughs and lead the way in brain health.

Our deep expertise in brain circuitry and demonstrated leadership in $GABA_A$ and NMDA receptor pathways have generated a robust portfolio of programs, including six Sage invented new chemical entities in development across 11 or more possible indications. We are progressing a promising and targeted pipeline with the goal of being able to launch new drugs or indications for years to come.

We have exciting milestones on the horizon for 2023. Last year, we submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) seeking approval of zuranolone as a 14-day, rapid-acting, once-daily, oral treatment in adults with major depressive disorder (MDD) and postpartum depression (PPD). The FDA has granted the application priority review with a resulting Prescription Drug User Fee Act (PDUFA) action date of August 5, 2023. If review timelines are met and zuranolone is approved, we expect a potential launch near the end of 2023. We are laser focused on preparing for this potential launch with our collaborators at Biogen and have made important progress in building our commercial capabilities over the last year. With Biogen, we are dedicated in our efforts to continue to advance our zuranolone activities with the goal of gaining approval and being able to offer a medicine with the potential to treat people with MDD and PPD rapidly and improve their symptoms.

We and Biogen also continue to make advancements in the development of SAGE-324, a next-generation positive allosteric modulator of $GABA_A$ receptors. We believe SAGE-324 holds significant potential in the treatment of neurological conditions like essential tremor, or ET, and we anticipate completing enrollment in the ongoing Phase 2b KINETIC 2 dose-ranging study late this year.

In our wholly owned pipeline, we are excited by the progress we've made with SAGE-718, our first-in-class NMDA receptor positive allosteric modulator being evaluated as an oral therapy in disorders where impairment of cognition is one of the main drivers of disability. Following encouraging early findings with SAGE-718, we are now focused on advancing multiple studies across Huntington's disease (HD), Alzheimer's (AD) and Parkinson's (PD) diseases. We believe that SAGE-718 holds the potential to provide meaningful symptomatic improvement in cognitive function early in disease so that patients may be able to maintain independence longer. We are also continuing to advance several programs in our early-stage pipeline, which together with our ongoing development engine, represent a key element of our long-term strategy to generate value.

The time is now to unleash the potential of our science and make a meaningful impact on the lives of millions. Our mission is to advance treatments for brain health and deliver what matters most to patients. We are investigating novel mechanisms of brain function that we believe can be important to unlocking breakthrough therapies. The strength of our execution lies with the passion of our employees, a diverse team focused on acting with urgency to meet the needs of patients. I am incredibly proud of how far we've come, and I am confident that together we can achieve the vision we set out to do. Thank you for your support as we aim to pioneer solutions to deliver life-changing brain health medicines, so every person can thrive. Our work depends on contributions from dedicated health care providers, empowered patients and patient advocates, and Sage's outstanding team and collaborators who work with passion and urgency every day.

Barry Greene
Chief Executive Officer
Sage Therapeutics

ANNUAL MEETING
The annual meeting of stockholders will be held virtually on Thursday, June 15, 2023, at 8:30 a.m. Eastern Time. Any stockholder as of the record date for the annual meeting may listen to the annual meeting and participate live via webcast at www.virtualshare-holdermeeting.com/SAGE2023.

INDEPENDENT AUDITORS
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101 Seaport Boulevard, Suite 500
Boston, MA 02110
(617) 530–5000

INVESTOR INQUIRIES
ir@sagerx.com

STOCK LISTING
Nasdaq: SAGE

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

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

SEC FORM 10-K
A copy of Sage's annual report on Form 10-K filed with the Securities and Exchange Commission is available free of charge from the company's Investor Relations Department by emailing ir@sagerx.com.

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, 2022

OR

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

For the transition period from _____ to

Commission file number: 001-36544

Sage Therapeutics, Inc.

(Exact Name of Registrant as Specified in its Charter)

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

(617) 299-8380

(Registrant's Telephone Number, Including Area Code)

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.0001 per share	SAGE	The 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 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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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 as of June 30, 2022 was approximately $1,685,744,591, 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 8, 2023, there were 59,717,608 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 2023 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, 2022. 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", "believes", "estimates", "predicts", "potential", "continue" or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our views as to the potential for approval by the U.S. Food and Drug Administration, or FDA of our new drug application, or NDA, for zuranolone (SAGE-217) as a treatment for major depressive disorder, or MDD, and postpartum depression, or PPD; our belief in the adequacy of the data we submitted in support of our NDA for zuranolone; the expected review timelines of such NDA; and the potential for future launch and commercialization of zuranolone in MDD and/or PPD, and the potential timing of such activities, if our NDA is approved;
- our views as to the potential for zuranolone for the treatment of MDD and PPD, if approved, including the potential product profile and treatment benefit, our commercialization strategy, plans, and expectations and the potential for zuranolone to be developed in additional indications;
- our plans for the development of our other product candidates for the treatment of brain health diseases and disorders, and potentially for other indications; our plans with respect to other research and development activities; and expected timelines for our planned activities;
- 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 belief as to potential outcomes of our clinical development and commercialization activities;
- our views as to potential future results of our ongoing commercialization efforts in the U.S. with respect to ZULRESSO® (brexanolone) CIV injection, which is approved in the U.S. for the treatment of postpartum depression, or PPD, in adults;
- our plans and potential outcomes with respect to interactions with regulatory authorities;
- our plans for and the potential costs, benefits and outcomes of our existing collaborations with Biogen MA Inc., or BIMA, and Biogen International GmbH, or, together with BIMA, Biogen, and Shionogi & Co., Ltd., or Shionogi, and our plans for and potential outcomes of any additional business development efforts;
- our plans and expectations with respect to the potential development of any product or product candidate for markets outside the U.S.;
- our expectations and estimates regarding: the level of expenses we may incur in connection with our activities; use of cash and projected cash on hand at any given timepoint; timing of future cash needs; capital requirements; sources of future financings; timing of receipt of potential milestone payments; and our ability to obtain additional financing when needed to fund future operations;
- our expectations with respect to the availability of supplies of ZULRESSO or of zuranolone and our other product candidates, and the expected performance of our third-party manufacturers, including conformity with applicable regulatory requirements;
- 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 and the potential size of the market for ZULRESSO in PPD, for zuranolone in MDD and PPD, if approved, and for our other product candidates in the indications we are pursuing or plan to study;
- the potential for our current product and current or future product candidates, if successfully developed and approved, for the indications and in the markets for which they are approved and our ability to serve those markets;

- the potential for success of competing products that are or become available for PPD or MDD or any of the other indications that we are pursuing or may pursue in the future with our products and our product candidates;
- the impact of changes to the macroeconomic environment on our activities, business and results of operations, and the potential success of our efforts to address or mitigate such impact; 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, among other things, 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 we provide in this Annual Report. Unless otherwise expressly stated, we obtained this industry and 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.

Summary of Risks Related to our Business

Our business, prospects, financial condition, and operating results are subject to numerous risks and uncertainties that you should be aware of before making an investment decision, as more fully described under Part I, Item 1A, Risk Factors and elsewhere in this Annual Report. These risks may include, but are not limited to, the following:

- Our future business prospects depend heavily on our ability, with our collaborator Biogen, to gain regulatory approval of zuranolone (SAGE-217) for the treatment of adults with MDD and PPD, and to successfully commercialize zuranolone in those indications, if approved. While our NDA for zuranolone is currently under review by the FDA, we cannot be certain that the FDA will grant approval of zuranolone in the indications we are seeking. The FDA may find that the design and results of our development program are not sufficient for regulatory approval of zuranolone for the treatment of MDD and PPD or may decline to approve our NDA for other reasons. Although we have been granted priority review, the FDA may not meet expected review timelines. Even if zuranolone is approved as a treatment for MDD and PPD, we may not be successful in our commercialization efforts. Any setback or delay in obtaining regulatory approval for zuranolone or in our ability to commence marketing of zuranolone, if approved, may have a material adverse effect on our business and prospects.
- Our future business prospects also depend heavily on our ability to successfully develop and gain regulatory approval of other product candidates beyond zuranolone. We cannot be certain that we or our collaborators, where applicable, will be able to initiate new clinical trials, complete ongoing clinical trials, or announce results of ongoing or future clinical trials of our other product candidates on the timelines we expect or at all, or that the results of our development programs will be positive or sufficient to file for regulatory approval. Decisions or actions of the FDA or other regulatory agencies may adversely affect our plans, progress or results at any stage of development. We cannot be certain that we or our collaborators will be able to successfully file or obtain regulatory approval for, or successfully commercialize, if approved, any such product candidates on the timelines we expect or at all. Any setback or delay in obtaining regulatory approval for any of 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 may never be able to generate meaningful revenues from sales of ZULRESSO® (brexanolone) CIV injection, or revenues at levels or on timing necessary to support our investment and goals.
- If the affected populations for indications our products and product candidates are targeting, including the addressable markets within such populations, or the number of patients within such markets who are actually treated with our products, including zuranolone, if successfully developed and approved, are smaller than we anticipate, or our other assumptions with respect to the potential markets for our products and product candidates are incorrect, our ability to achieve profits from the commercialization of such products, if approved, at the levels or on the timing we expect could be materially adversely impacted.
- Positive results from 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 in the same indications or other indications. Interim results from non-clinical studies and clinical trials may not be predictive of results of such non-clinical studies or clinical trials once completed. The results of non-clinical studies or clinical trials of our product candidates at any stage may not support further development or may not be sufficient to file for and obtain regulatory approval.
- If serious adverse events or other undesirable side effects are identified during the use of any of our marketed products or product candidates, including during commercial use, in clinical trials or under an expanded access program, if initiated for any of our products or product candidates, such events may adversely affect market acceptance or result in other significant negative consequences for an approved product; delay or prevent further development or regulatory approval with respect to product candidates; or cause regulatory authorities to require labeling statements, such as boxed warnings, or a Risk Evaluation and Mitigation Strategy, on approved products.
- We rely completely on third-party suppliers to manufacture commercial supplies of ZULRESSO and clinical drug supplies for our product candidates and intend to rely on third-party manufacturers for commercial supplies of zuranolone, if approved, and of any of our other product candidates that are successfully developed and approved for marketing. Any impairment of the ability of our third-party suppliers to supply product or to meet applicable regulatory standards may significantly negatively impact our ability to achieve our goals and plans and to meet the expectations for our business.
- Zuranolone, if approved, and any of our other current product candidates, if successfully developed and approved, and other future products, if any, may not have the profile we expect in clinical practice after launch or may not achieve broad market acceptance for the approved indications, or reimbursement at sufficient levels, and the results of our commercialization efforts may not meet our expectations, which may limit the revenue that we generate from sales of such products.
- Competing therapies may exist or could emerge that adversely affect the amount of revenue we are able to generate from the sale of ZULRESSO, zuranolone, if approved, or any of our other current or future product candidates, if successfully developed and approved.
- Our existing collaborations with Biogen and Shionogi, and any future collaborations, may not lead to the successful development or regulatory approval of product candidates or commercialization of products. Our collaborators may have competing priorities, conflicting incentives, or different views than us on key decisions, including appropriate program spending, that may hamper or delay our development and commercialization efforts or increase our costs. Our business may be adversely affected if any of our collaborators fails to perform its obligations or terminates our collaboration in whole or in part.
- We may not be successful in our efforts to identify new targets, generate new compounds, and successfully bring such new compounds through investigational new drug application-enabling non-clinical studies. 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.
- If we are unable to adequately protect our proprietary technology, or obtain and maintain issued patents that are sufficient to protect our products or 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.
- For certain of our products and product candidates, we are dependent on licensed intellectual property. If we were to lose our rights to licensed intellectual property, or if we are not able to obtain licenses to intellectual property we may determine we need in the future, we may not be able to continue developing or commercializing certain of our products or product candidates, if approved.

- Existing or future laws, regulations, executive orders or policies aimed at reducing healthcare costs may have a material adverse effect on our business or results of operations.
- We are subject to healthcare laws and regulations, which could expose us to the risk of criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings if we or our employees are alleged or determined not to have complied with such laws and regulations.
- We have not generated significant revenue to date. We have incurred significant operating losses since our inception, and anticipate that we will incur losses for the foreseeable future.
- We may need to raise additional funding in the future, which may not be available on acceptable terms, or at all. Raising additional capital, even opportunistically, may cause dilution to our existing stockholders, restrict our operations or require us to relinquish valuable rights.
- The changes to the macroeconomic environment, including the healthcare and vendor staffing shortages and disruption to the U.S. healthcare system that began as a result of the COVID-19 pandemic, may continue to adversely impact our business, including our sales of ZULRESSO and our initiation, conduct and completion of clinical trials.
- The Inflation Reduction Act of 2022 and other existing, pending or future federal and state reforms aimed at reducing healthcare costs, including pricing and reimbursement of pharmaceutical products, may in the future result in reduced reimbursement and access for our approved products or cause us to curtail certain development plans because of concerns about commercial viability, any of which could adversely affect our ability to commercialize our products and generate revenue and negatively impact our business, results of operations and financial condition.

PART I

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

Item 1. Business

Overview

We are a biopharmaceutical company with a mission to pioneer solutions to deliver life-changing brain health medicines, so every person can thrive. We are currently targeting diseases and disorders of the brain with three key focus areas: depression, neurology and neuropsychiatry. Our focus as a company is on brain health, and we are currently targeting two critical central nervous system, or 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.

Our first product, ZULRESSO® (brexanolone) CIV injection, is approved in the U.S. for the treatment of postpartum depression, or PPD, in adults. We launched ZULRESSO commercially in the U.S. for the treatment of PPD in June 2019. ZULRESSO may only be administered in qualified medically-supervised healthcare settings. Brexanolone is chemically identical to allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors.

We also are developing a portfolio of other novel compounds that target $GABA_A$ receptors including our most advanced product candidate, zuranolone (SAGE-217). Zuranolone is a novel oral compound being developed for the treatment of major depressive disorder, or MDD, and PPD. In December 2022, we, and our collaboration partner, Biogen, completed submission of a new drug application, or NDA, to the U.S. Food and Drug Administration, or FDA, seeking approval of zuranolone for the treatment of both MDD and PPD. The NDA was accepted for filing and granted priority review by the FDA in February 2023, with a Prescription Drug User Fee Act, as amended, or PDUFA, target action date of August 5, 2023. The FDA granted Fast Track designation to zuranolone for the treatment of PPD in early 2022 and previously granted zuranolone Breakthrough Therapy designation and Fast Track designation for the treatment of MDD. Zuranolone is a neuroactive steroid that, like brexanolone, is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extrasynaptic $GABA_A$ receptors. We may in the future develop zuranolone for other affective disorders.

To date, we have completed six pivotal clinical trials of zuranolone, four in MDD and two in PPD. The completed pivotal trials evaluating zuranolone for the treatment of PPD and three of the four completed pivotal trials evaluating zuranolone for the treatment of MDD met their primary endpoints.

We are jointly developing zuranolone and another of our late-stage compounds, SAGE-324, in the U.S. with Biogen MA Inc., or BIMA, and Biogen International GmbH, or, together with BIMA, Biogen, under a collaboration and license agreement, or the Biogen Collaboration Agreement, that became effective in December 2020.

Under the Biogen Collaboration Agreement, we will also jointly commercialize products containing zuranolone, which we refer to as Licensed 217 Products, and products containing SAGE-324, which we refer to as Licensed 324 Products, with Biogen in the U.S. if our development efforts are successful. We refer to the Licensed 217 Products and Licensed 324 Products individually as a Product Class and collectively as the Licensed Products. In addition, we have granted Biogen sole rights to develop and commercialize the Licensed Products outside the U.S., other than in Japan, Taiwan and South Korea, or the Shionogi Territory, with respect to zuranolone, where we have granted rights to Shionogi & Co., Ltd., or Shionogi. We refer to the territories outside the U.S. to which Biogen has rights under the Biogen Collaboration Agreement with respect to the applicable Licensed Product as the Biogen Territory.

We also have a collaboration agreement with Shionogi for the development of zuranolone in the Shionogi Territory. In September 2021, Shionogi reported completion of a Phase 2 clinical trial of zuranolone for the treatment of patients

with moderate to severe MDD in Japan, which Shionogi reported achieved its primary endpoints. Shionogi has also reported that it is conducting two Phase 3 trials of zuranolone for the treatment of patients with moderate to severe MDD as a monotherapy and as an add-on to other antidepressants, and announced that, pending results from these trials, it is aiming to submit an NDA to the Pharmaceuticals and Medical Devices Agency in Japan in the first quarter of 2024 seeking approval of zuranolone for the treatment of MDD.

SAGE-324 is a novel $GABA_A$ receptor positive allosteric modulator intended for chronic oral dosing. We are currently enrolling patients with essential tremor in a Phase 2b placebo-controlled dose-ranging clinical trial of SAGE-324, known as the KINETIC 2 Study. In May 2022, we also initiated an open-label Phase 2 clinical trial designed to evaluate the long-term safety and tolerability of SAGE-324 in patients with essential tremor, with incidence of treatment-emergent adverse events as the primary endpoint. This is intended to be a multi-year clinical trial, and will initially be open to rollover patients from other SAGE-324 clinical trials in patients with essential tremor, including the KINETIC 2 Study. We believe SAGE-324 also has potential for the treatment of a number of other neurological conditions, including epilepsy and Parkinson's disease. Additional development plans for SAGE-324 will be determined as part of our strategic collaboration with Biogen.

Our second area of focus for development is novel compounds that target the NMDA receptor. Our lead product candidate selected in this area is SAGE-718, an oxysterol-based positive allosteric modulator of the NMDA receptor, which we are exploring in certain cognition-related disorders associated with NMDA receptor dysfunction, including cognition dysfunction associated with diseases such as Huntington's disease, Parkinson's disease and Alzheimer's disease. The FDA has granted SAGE-718 Fast Track designation as a potential treatment for patients with Huntington's disease. SAGE-718 is currently being studied in several ongoing clinical trials, including the placebo-controlled Phase 2 DIMENSION Study, the placebo-controlled Phase 2 SURVEYOR Study, and the Phase 3 open-label PURVIEW Study evaluating patients with Huntington's disease cognitive impairment; the double-blind placebo-controlled Phase 2 PRECEDENT Study evaluating SAGE-718 in patients with mild cognitive impairment due to Parkinson's disease; and the randomized placebo-controlled Phase 2 LIGHTWAVE Study evaluating SAGE-718 in patients with mild cognitive impairment and mild dementia due to Alzheimer's disease.

We have other programs at earlier stages of development with a focus on both acute and chronic brain health disorders. We expect to continue our work 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. We also believe that we may have the opportunity to use our scientific approach to explore targets beyond the $GABA_A$ and NMDA receptor systems and to develop compounds in areas of unmet need outside of brain health.

Our Strategy

Our goal is to build a top-tier biopharmaceutical company that is the leader in developing and commercializing life-changing brain health medicines. Our current focus is on building on our opportunities in depression, neurology, and neuropsychiatry. Key elements of our strategy are to:

- gain regulatory approval of zuranolone for the treatment of PPD and MDD in the U.S., continue permitted pre-launch and launch-readiness activities for zuranolone, launch and commercialize zuranolone, if approved, and potentially advance development of zuranolone in additional indications, all as part of our strategic collaboration with Biogen;
- continue our commercialization efforts with respect to ZULRESSO for the treatment of PPD in the U.S., with a primary focus in geographies that have existing, active ZULRESSO treating sites;
- complete the ongoing and planned clinical trials of SAGE-324 as part of our strategic collaboration with Biogen;
- complete ongoing and planned clinical trials of SAGE-718;

- support our collaboration with Biogen with respect to zuranolone and SAGE-324 in the U.S., and support Biogen's development of zuranolone and SAGE-324 in the Biogen Territory and Shionogi's development of zuranolone in the Shionogi Territory;
- advance our earlier-stage compounds;
- continue our research and development efforts to evaluate the potential for our existing product candidates for the treatment of additional indications or in new formulations;
- identify new targets, and generate and test new compounds and product candidates, with a focus on indications where we believe we can make well-informed, rapid go/no-go decisions, with the goal of developing a diversified portfolio of assets with differentiated features;
- prepare and file NDAs with the FDA, and conduct permitted pre-launch activities with respect to any of our other product candidates that we believe have been successfully developed;
- commercialize any product candidates for which we obtain regulatory approval, including the manufacture of commercial supplies;
- continue to add personnel at the appropriate time, as our efforts and activities progress, including personnel to support ongoing zuranolone commercialization efforts, such as launch planning, permitted payor engagements, scientific exchange, disease awareness education, and ongoing product development, and to support launch of zuranolone in MDD and PPD, if approved;
- evaluate the market potential and regulatory pathways for our product candidates beyond zuranolone and SAGE-324 in the European Union, or EU, and other jurisdictions outside the U.S., and determine how best to move forward where and when it may make business and strategic sense;
- continue to build, maintain, defend, leverage, and expand our intellectual property portfolio, including by utilizing 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; and
- continue to explore opportunities to establish licenses, collaborations, or other agreements or alliances with other biotechnology and pharmaceutical companies, at the appropriate time, where we believe a collaboration will add significant value to our efforts, including through capabilities, infrastructure, speed or financial contributions, or to acquire new compounds, product candidates or products if we believe such opportunities will help us achieve our goals or meet other strategic objectives.

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, 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 currently 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 diseases and disorders of the brain.

We utilize our proprietary chemistry capabilities to design and identify drug candidates that target critical CNS proteins and have properties aligned 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.

Our focus as a company is on brain health, and we are currently targeting 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 brain disorders.

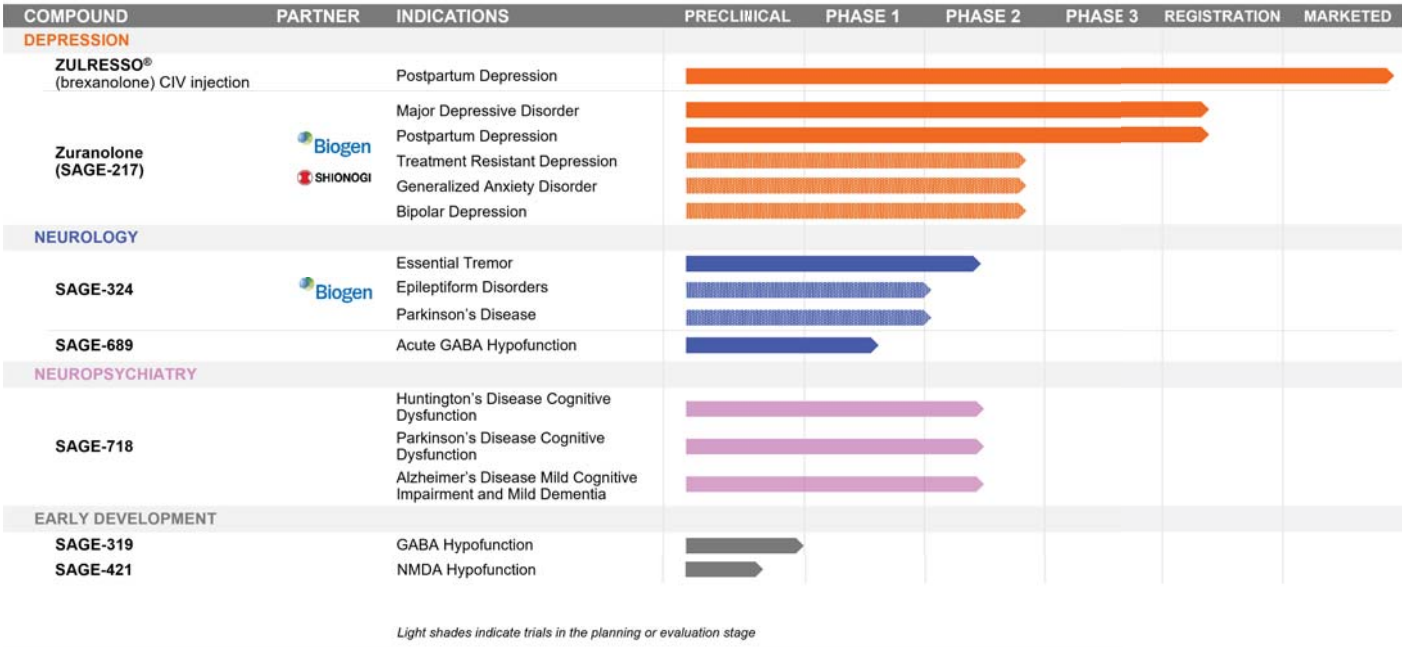
Our proprietary chemistry platform is currently centered on our knowledge of the chemical scaffolds of endogenous neuroactive steroids. We have leveraged this platform to assemble a chemistry portfolio of greater than 10,000 compounds. We believe our proprietary chemistry platform allows us to:

- 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 diseases and disorders of the brain where we believe 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 product and product candidate portfolio as of the filing date of this Annual Report.



ZULRESSO® (Brexanolone) CIV Injection

Our first product, ZULRESSO, is a proprietary IV formulation of brexanolone. Brexanolone is chemically identical to allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors. We launched ZULRESSO commercially in the U.S. in June 2019 for the treatment of PPD in adults, after approval by the FDA and completion of controlled substance scheduling of brexanolone by the U.S. Drug Enforcement Administration, or DEA, and incorporation of the scheduling into the FDA-approved label and other product information. The DEA placed ZULRESSO into Schedule IV of the Controlled Substances Act, or CSA. ZULRESSO is administered as a continuous infusion given over two and a half days. Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness during the ZULRESSO infusion, ZULRESSO must be administered in a medically-supervised healthcare setting that has been certified under a Risk Evaluation and Mitigation Strategy, or REMS, program and meets the other requirements of the REMS program, including requirements related to monitoring of the patient during the infusion. Patients who are prescribed ZULRESSO are required to enroll in a registry which may allow us to compile additional information to further our understanding of the risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO and management of the risk. Given the mode and setting of administration of ZULRESSO and the requirements of the REMS program, ZULRESSO has been administered to date primarily to treat women with severe PPD, and we expect that to continue to be the case.

PPD is one of the most common medical complications during and after pregnancy, and is characterized by depressive symptoms that may occur during pregnancy or following childbirth up to 12 months. 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 mothers experiencing symptoms of PPD each year vary state-to-state from 9.7% to 23.5%, with an overall average of 13.2%. Based on these data, we estimate that approximately 500,000 women in the U.S. each year may experience symptoms of PPD, and approximately 28% 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 one of the leading causes of maternal death following childbirth.

ZULRESSO is the only pharmacological therapy specifically approved for PPD. The 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. These data led to our interest in evaluating allosteric modulators of the $GABA_A$ receptor—such as brexanolone and zuranolone—for the treatment of PPD.

The approval of ZULRESSO in the U.S. was based on positive results from our HUMMINGBIRD Phase 3 clinical program, which was comprised of two multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase 3 clinical trials designed to evaluate the safety and effectiveness of brexanolone in women with PPD, with supportive evidence from a Phase 2 clinical trial of brexanolone in PPD. Results from the HUMMINGBIRD Phase 3 clinical program were published in the September 22, 2018 issue of *The Lancet*.

Zuranolone (SAGE-217)

Our most advanced product candidate is zuranolone (SAGE-217), a novel oral compound being developed for the treatment of MDD and PPD. In December 2022, we and our collaboration partner, Biogen, completed submission of an NDA to the FDA seeking approval of zuranolone for the treatment of MDD and PPD. The NDA was accepted for filing and granted priority review by the FDA in February 2023, with a PDUFA target action date of August 5, 2023. Zuranolone is a neuroactive steroid that, like brexanolone, is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extrasynaptic $GABA_A$ receptors. We also believe zuranolone has potential in other indications such as treatment resistant depression, bipolar depression and generalized anxiety disorder. We are jointly developing zuranolone in the U.S. with Biogen under the Biogen Collaboration Agreement that became effective in December 2020, and will jointly commercialize zuranolone in the U.S. if our development efforts are successful and zuranolone is approved in the U.S. The Biogen Collaboration Agreement covers any products incorporating zuranolone. We have granted Biogen sole rights to develop and commercialize the Licensed 217 Products outside the U.S., other than in the Shionogi Territory, where we have granted rights to Shionogi. The FDA granted Fast Track designation to zuranolone for the treatment of PPD in early 2022, and previously granted zuranolone Breakthrough Therapy designation and Fast Track designation to zuranolone for the treatment of MDD.

MDD is a serious mental health disorder commonly characterized by symptoms of depressed mood and/or loss of interest in pleasurable activities causing impairment in daily life. MDD is characterized by a period of depressive symptoms lasting at least two weeks and is associated with changes in affect, cognition, and function. 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 MDD also suffer from anxiety symptoms as a symptom of their depression 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 for the treatment of MDD, but many patients do not adequately respond to existing treatments. According to estimates, approximately 21 million adults in the U.S. reported at least one major depressive episode in 2021. Among U.S. adults reporting at least one major depressive episode in 2021, approximately 12.6 million (61%) received treatment within the prior year; and 10.5 million received pharmacologic treatment. Research conducted between April 2020 and December 2022 reported a three- to four-fold increase in symptoms of depression among adults in the U.S. compared to prior to the COVID-19 pandemic. 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. In 2018, the incremental economic burden of MDD was an estimated $326 billion in the U.S.

To date, we have completed six pivotal clinical trials evaluating zuranolone, four in MDD and two in PPD, the results of which have been previously disclosed. The completed pivotal trials evaluating zuranolone for the treatment of PPD and three of the four completed pivotal trials evaluating zuranolone for the treatment of MDD met their primary endpoints. We announced results from the following clinical trials of zuranolone in either 2021 or 2022:

- **SKYLARK Study (completed)**

  In June 2022, we announced that the SKYLARK Study, a Phase 3 placebo-controlled clinical trial evaluating a two-week course of zuranolone 50 mg in women with PPD, met its primary and all key secondary endpoints. Women treated with zuranolone 50 mg (n=98) demonstrated a statistically significant and clinically meaningful improvement in depressive symptoms at Day 15, the primary endpoint, and at Days 3, 28, and 45, key secondary endpoints, in each case compared to women treated with placebo (n=97) as measured by a change from baseline in the 17-item Hamilton Rating Scale for Depression, or HAMD-17, total score. The least-squares mean change from baseline (standard error) in HAMD-17 total score at Day 15 for women who received zuranolone 50 mg was -15.6 (0.82) compared with -11.6 (0.82) for women who received placebo (LS mean difference -4.0 points; p=0.0007). Zuranolone 50 mg was generally well-tolerated and demonstrated a safety profile consistent with that observed in prior clinical studies. In women who experienced treatment emergent adverse events, or TEAEs, the majority were mild to moderate in severity. The most common treatment emergent adverse events (>5% in the zuranolone 50 mg arm) were somnolence, dizziness, sedation, headache, diarrhea, nausea, urinary tract infection and COVID-19.

- **CORAL Study (completed)**

  In February 2022, we announced results from the CORAL Study, a placebo-controlled Phase 3 clinical trial evaluating a two-week course of zuranolone 50 mg, when co-initiated with a newly administered open-label ADT, compared with open-label standard of care ADT co-initiated with placebo, as an acute rapid response treatment in patients with MDD. Patients in the clinical trial received zuranolone 50 mg co-initiated with an open-label standard of care ADT or open-label standard of care ADT co-initiated with placebo once nightly for 14 days followed by continuation of the ADT for an additional short-term follow-up period. The study results showed a mean change from baseline in the HAMD-17 total score of -8.9 ± 0.39 (n=210) at Day 3 for patients in the zuranolone co-initiated with ADT arm compared with -7.0 ± 0.38 (n=215) mean change from baseline for patients in the ADT co-initiated with placebo arm. The key secondary endpoint measured the treatment effect over the two-week treatment period at all scheduled visits (measured using equal weighted means for Days 3, 8, 12 and 15 of the study). The mean change over the treatment period for patients who received zuranolone co-initiated with an ADT was -11.7 ±0.40 (n=210) compared with -10.1 ±0.39 (n=215) for patients who received ADT co-initiated with placebo. Other secondary endpoints demonstrated a statistically significant reduction in HAMD-17 score in the zuranolone co-initiated with ADT arm compared to the ADT arm at Days 8 and 12, while Day 15 demonstrated numerical superiority and Day 42 showed equivalence. The results also indicate that zuranolone 50 mg co-initiated with a standard of care ADT was generally well-tolerated with no new safety signals identified. The majority of patients in the study experienced TEAEs that were mild or moderate in severity, consistent with previous data. The adverse events occurring 10% or higher in either treatment arm (zuranolone with ADT vs. ADT with placebo) were somnolence (18.4% vs. 8.3%), dizziness (13.2% vs. 7.3%), headache (11.8% vs. 14.7%), and nausea (9.0% vs 23.4%). The percentage of patients reporting TEAEs leading to drug discontinuation was 6.6% in the zuranolone co-initiated with an ADT arm, and 3.7% in the ADT co-initiated with placebo arm, respectively. The percentage of patients reporting TEAEs leading to discontinuation of ADT were 7.5% in the zuranolone co-initiated with an ADT arm, and 5.5% in the ADT co-initiated with placebo arm, respectively.

- **WATERFALL Study (completed)**

  In June 2021, we announced that the WATERFALL Study, a pivotal, Phase 3, double-blind, randomized, placebo-controlled clinical trial evaluating the efficacy and safety of zuranolone 50 mg in adults aged 18 to 64 years with MDD, met its primary endpoint. In the WATERFALL Study, zuranolone 50 mg showed a statistically significant and clinically meaningful reduction in depressive symptoms as measured by HAMD-17 total score at Day 15 (p-value=0.0141) compared to placebo. Patients in the zuranolone arm with a

decrease in HAMD-17 baseline score of ≥50% at Day 15 retained on average 86% of their HAMD-17 improvement at Day 42 (four weeks after dosing ended). A rapid onset of treatment effect was seen in the HAMD-17 results at Days 3, 8 and 12. Zuranolone was generally well-tolerated in the WATERFALL Study and demonstrated a safety profile consistent with previous clinical studies. The rate of TEAEs reported in the zuranolone group was 60.1% (161/268) compared to the placebo group at 44.6% (120/269). The majority of the TEAEs reported were mild to moderate. The most common TEAEs that were reported by ≥ 5% of patients treated with zuranolone (rates compared to placebo) included somnolence 15.3% (3.0%), dizziness 13.8% (2.2%), headache 10.8% (7.8%), and sedation 7.5% (0.4%). These events predominantly occurred during the 14-day treatment period. Throughout the study, a total of four patients reported serious adverse events, two (0.7%) each in the zuranolone and placebo groups; no deaths occurred in the study. The percent of patients reporting TEAEs leading to drug discontinuation was 3.4% (9/268) and 1.5% (4/269), in the zuranolone and placebo groups, respectively.

- **SHORELINE Study (ongoing)**

  We are also conducting an open-label Phase 3 clinical trial, known as the SHORELINE Study, evaluating the safety, tolerability, and need for repeat dosing with zuranolone in adults with MDD, in which patients receive an initial two-week course of zuranolone and those who have a clinical response (decrease in HAMD-17 baseline score of ≥50%) from the first cycle have the opportunity to be followed for up to one year and are eligible to receive as-needed retreatment during the follow-up period. The need for repeated dosing is assessed every 14 days based on the results of a patient-reported Patient Health Questionnaire-9 score (≥10) and HAMD-17 assessment (≥20). The protocol of the clinical trial requires a minimum of 56 days between zuranolone 14-day courses, to allow for a maximum of five treatments during the follow-up period.

  In December 2021, we reported 12-month data from the 50 mg cohort of the SHORELINE Study. Data reported for this cohort of patients (n=199), showed that a majority of the patients who had a clinical response to the initial 14-day course received only one two-week course of treatment in total during their time in the study and nearly 80% received only one or two treatment courses in total. Specifically, of the 146 patients who had a clinical response to the initial 2-week treatment, 80 (54.8%) patients received only the single initial zuranolone course during their time in the study, while 36 (24.7%) received a total of two course, 15 (10.3%) received a total of three courses, 10 (6.8%) received a total of four courses and 5 (3.4%) received a total of five courses in total. Zuranolone 50 mg was generally well-tolerated with no new safety finding or trend identified in the long-term safety data available to date on patients followed up to one year who received a single or repeat dosing courses. Safety was assessed during treatment and in between treatment courses and over multiple treatment courses to help inform tolerability over time. Over the entire study, 137 of 199 (68.8%) patients who initiated treatment with zuranolone 50 mg reported at least one TEAE, similar to the previously reported 30 mg cohort. The most common TEAEs that were reported by ≥ 5% of patients treated with zuranolone were somnolence (32; 16.1%), dizziness (30; 15.1%), headache (25; 12.7%), sedation (20; 10.1%), insomnia (14; 7.0%), nausea (13; 6.5%), and tremor (11; 5.5%). The majority of patients reported TEAEs with a maximum severity of mild to moderate.

  The data from the 50 mg cohort is consistent with 12-month data we reported in March 2021, from the completed 30 mg cohort of the SHORELINE Study. In the 30 mg zuranolone cohort, approximately 70% of participants with a clinical response to an initial 2-week treatment required at most one additional zuranolone treatment during their time in the 12-month study. Of the 489 patients who responded to the initial 14-day treatment course and continued in the study, 210 (42.9%) patients received only the single initial zuranolone course during their time in the study, while 125 (25.6%) received a total of two courses, 58 (11.9%) received a total of three courses, 53 (10.8%) received a total of four courses, and 43 (8.8%) received a total of five courses. In the 30 mg cohort, 368 (51%) patients reported at least one TEAE. The most common TEAEs that were reported by ≥ 5% of patients treated with zuranolone were somnolence (86; 11.9%), headache (103; 14.2%), and dizziness (54; 7.4%). Most of the reported TEAEs were mild or moderate.

  Enrollment in the 50 mg cohort of the SHORELINE Study has been completed and the study is ongoing.

Shionogi has reported that it is conducting two Phase 3 trials of zuranolone for the treatment of patients with moderate to severe MDD as a monotherapy and as an add-on to other antidepressants, and announced that, pending results from these trials, it is aiming to submit an NDA to the Pharmaceuticals and Medical Devices Agency in Japan in the first quarter of 2024 seeking approval of zuranolone for the treatment of MDD. In September 2021, Shionogi announced that it achieved the primary endpoints from a Phase 2 clinical trial of zuranolone for the treatment of patients with moderate to severe MDD in Japan. The data reported by Shionogi for this Phase 2 study showed significant improvement over placebo from day three (first observation) to day 15 (end of administration) of change in HAMD-17 total score from baseline in a group of 85 patients who received zuranolone 20 mg once daily for two weeks and a group of 82 patients who received 30 mg once daily for two weeks, as compared to 82 patients who received the placebo. Shionogi reported that all adverse events were mild or moderate. Shionogi previously completed a Phase 1 clinical trial in Japan to evaluate the safety and tolerability of zuranolone in Japanese and Caucasian subjects.

We may consider additional development opportunities for zuranolone as part of the Biogen collaboration.

SAGE-324

In addition to zuranolone, we have a portfolio of other novel compounds that target $GABA_A$ receptors, including SAGE-324, which we are jointly developing with Biogen under the Biogen Collaboration Agreement. SAGE-324 is a novel $GABA_A$ receptor positive allosteric modulator intended for chronic oral dosing. In April 2021, we and Biogen reported topline results from our placebo-controlled Phase 2 clinical trial evaluating the safety and efficacy of SAGE-324 for the treatment of essential tremor, known as the KINETIC Study. Essential tremor is a neurodegenerative condition characterized by rhythmic trembling most commonly of the upper limbs, including the hands. The head, voice, legs or trunk may also be affected. Symptoms generally evolve over time, are persistent, and affect patients' ability to function independently. Essential tremor is among the most common movement disorders, estimated to affect more than 6 million adults in the U.S. Adults of all ages can be impacted by essential tremor, though risk increases with age. First-line treatments for essential tremor include β-adrenergic blocker propranolol and anticonvulsant primidone.

The Phase 2 KINETIC Study evaluating SAGE-324 for the treatment of adults with essential tremor (n=67 full analysis set) achieved its primary endpoint of a statistically significant reduction from baseline compared to placebo in The Essential Tremor Rating Assessment Scale, or TETRAS, Performance Subscale Item 4 upper limb tremor score on Day 29 (p-value=0.049), which corresponded to a 36% reduction from baseline in upper limb tremor amplitude in patients receiving SAGE-324 compared to a 21% reduction in patients receiving placebo. Patients were randomized 1:1 to receive SAGE-324 (60 mg) or matched placebo once daily in the morning. The trial evaluated treatment of SAGE-324 at the higher end of the dose range and the daily dose could be down-titrated to 45 mg or 30 mg. Activities of daily living, or ADL, scores showed a statistically significant correlation with upper limb tremor score at all timepoints. Although the clinical trial was not powered to fully examine TETRAS ADL, SAGE-324 was numerically superior to placebo at all time points during treatment. Reported TEAEs were generally consistent with the safety profile of SAGE-324 previously reported. The most common TEAEs that were reported by 10% or more of patients in the SAGE-324 treatment group and at a rate at least twice as high as that of patients in the placebo group were: somnolence 68%; dizziness 38%; balance disorder 15%; diplopia 12%; dysarthria 12%; and gait disturbance 12%. In the KINETIC Study, patients with a more severe tremor at baseline (at or above the median TETRAS Performance Subscale upper limb tremor Item 4 score of 12) (n=47) who received SAGE-324 demonstrated a statistically significant reduction (p-value=0.007) from baseline in TETRAS Performance Subscale Item 4 upper limb tremor score compared to placebo at Day 29, corresponding to a 41% reduction from baseline in upper limb tremor amplitude in patients receiving SAGE-324 compared to an 18% reduction for placebo.

A Phase 2b double-blind, randomized, placebo-controlled, dose-response study of SAGE-324 in patients with moderate to severe essential tremor, known as the KINETIC 2 Study, is currently enrolling patients and we expect to complete enrollment in late 2023. The primary aim of the KINETIC 2 Study is to evaluate different doses of SAGE-324 in reducing upper limb tremors. The primary endpoint of the study is change from baseline in TETRAS Performance Subscale Item 4 total score at Day 91. In May 2022, we initiated an open-label Phase 2 clinical trial designed to evaluate the long-term safety and tolerability of SAGE-324 in patients with essential tremor, with incidence of treatment-emergent adverse events as the primary endpoint. This is intended to be a multi-year clinical trial, and will initially be open to rollover patients from other SAGE-324 clinical trials in patients with essential tremor, including the KINETIC 2 Study.

We believe SAGE-324 also has potential for the treatment of a number of other neurological conditions, including epilepsy and Parkinson's disease.

We are jointly developing SAGE-324 in the U.S. with Biogen, and will jointly commercialize Licensed 324 Products with Biogen in the U.S. if our development efforts are successful and SAGE-324 is approved in the U.S. We have granted Biogen sole rights to develop and commercialize SAGE-324 outside the U.S. We may consider additional development plans and opportunities for SAGE-324 as part of our collaboration with Biogen.

SAGE-718

Our second area of focus is the development of novel compounds that target the NMDA receptor. Examples of indications involving NMDA receptor dysfunction include certain types, aspects or subpopulations of a number of diseases such as Huntington's disease, Parkinson's disease, Alzheimer's disease, depression, attention deficit hyperactivity disorder, schizophrenia, and neuropathic pain.

Our lead product candidate selected in this area is SAGE-718, an oxysterol-based positive allosteric modulator of the NMDA receptor, which we are exploring in certain cognition-related disorders associated with NMDA receptor dysfunction, including cognition dysfunction associated with diseases such as Huntington's disease, Parkinson's disease and Alzheimer's disease.

Huntington's disease

The FDA has granted SAGE-718 Fast Track designation as a potential treatment for Huntington's disease. SAGE-718 is currently being studied in three ongoing clinical trials in patients with Huntington's disease cognitive impairment:

- **DIMENSION Study**

  In February 2022, dosing commenced in the DIMENSION Study, a double-blind placebo-controlled Phase 2 clinical trial of SAGE-718 in patients with Huntington's disease cognitive impairment. The DIMENSION Study is designed to evaluate the efficacy of once-daily dosed SAGE-718 over three months.

- **SURVEYOR Study**

  In March 2022, we initiated the SURVEYOR Study, a placebo-controlled Phase 2 clinical trial of SAGE-718 in patients with Huntington's disease cognitive impairment, with a healthy volunteer component, with the goal of generating evidence linking efficacy signals on cognitive performance to domains of real-world functioning.

- **PURVIEW Study**

  In December 2022, we initiated the PURVIEW Study, a Phase 3 open-label study to evaluate the long-term safety and tolerability of SAGE-718 in patients with Huntington's disease cognitive impairment.

Parkinson's disease

In May 2021, we announced results from the 14-day dosing cohort, or Cohort A, of a Phase 2a open-label clinical trial of SAGE-718 evaluating patients with mild cognitive impairment due to Parkinson's disease, known as the PARADIGM Study. In Cohort A of the clinical trial, eight patients aged 50 to 75 years with mild cognitive impairment due to Parkinson's disease received 3 mg of SAGE-718 daily for 14 days. Patients showed performance improvements from baseline on multiple tests in the cognitive domain of executive function during the 14 days of treatment. Emerging signals on several measures also suggested improved performance from baseline on cognitive tests in the domains of learning and memory over a similar timeframe.

In October 2022, we presented additional results from the 28-day cohort, or Cohort B, of the open-label PARADIGM Study. In Cohort B of the clinical trial, seven patients aged 50 to 75 years with mild cognitive impairment due to Parkinson's disease received 3 mg of SAGE-718 daily for 28 days. Patients showed performance improvements

from baseline on multiple tests in the cognitive domain of executive function during the 28 days of treatment, as well as during the 14 day follow-up period. SAGE-718 was generally well-tolerated in both cohorts of the study; there were no serious adverse events reported, and no TEAEs were determined to be related to SAGE-718 or resulted in study drug discontinuation or withdrawal from the study. As expected, given its profile, SAGE-718 demonstrated neutral results in certain tests of attention and psychomotor speed.

In March 2022, we initiated a double-blind, placebo-controlled Phase 2 clinical trial of SAGE-718 in patients with mild cognitive impairment due to Parkinson's disease, known as the PRECEDENT Study. The PRECEDENT Study is designed to evaluate the safety and efficacy of SAGE-718 in patients with mild cognitive impairment due to Parkinson's disease over 42 days, followed by a controlled follow-up period.

Alzheimer's disease

In December 2021, we reported topline data from the LUMINARY Study, a Phase 2a open-label clinical trial of SAGE-718 in patients with mild cognitive impairment and mild dementia due to Alzheimer's disease (n=26 full analysis set), who received 3 mg of SAGE-718 daily for 14 days. The results showed performance improvements from baseline on five out of five unique tests in the cognitive domain of executive function and two out of four unique tests in the cognitive domains of learning and memory during the 14 days of treatment, consistent with positive signals seen in open-label clinical trials evaluating SAGE-718 as a treatment for cognitive impairment due to Parkinson's disease and Huntington's disease. Patients also showed performance improvement as measured by the Montreal Cognitive Assessment (MoCA) Test, a global measure of cognition, that reached statistical significance at Day 28 when compared to baseline in patients treated with SAGE-718. In certain tests of attention and psychomotor speed, SAGE-718 demonstrated neutral results. SAGE-718 was generally well tolerated in the LUMINARY Study. Seven subjects reported a total of 11 TEAEs, seven of which were considered related to the study treatment and all of which were rated as mild or moderate in severity. The most commonly reported TEAEs were headache (n=2) and constipation (n=2). In December 2022, we initiated the LIGHTWAVE Study, a randomized placebo-controlled Phase 2 clinical trial of SAGE-718 in patients with mild cognitive impairment and mild dementia due to Alzheimer's disease.

Further Exploration of $GABA_A$ and NMDA Receptors and New Areas of Interest

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 portfolio of novel $GABA_A$ receptor positive allosteric modulators includes SAGE-689, a product candidate in Phase 1 clinical development intended for intramuscular administration. We also have other compounds at earlier stages of development with a focus on both acute and chronic brain health disorders, including SAGE-319, an extrasynaptic $GABA_A$ receptor-preferring positive allosteric modulator, which we plan to move into Phase 1 clinical development. SAGE-319 is being evaluated for its potential use as an oral therapy in treating disorders of social interaction. We also have earlier stage compounds focused on NMDA receptor modulation, including SAGE-421, an NMDA receptor positive allosteric modulator that we plan to study for potential use in neurodevelopmental disorders and cognitive recovery and rehabilitation. 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 opportunities 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 brain health 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 therapies or previous therapies which have failed in development. We believe that we may also have the opportunity to use our scientific approach to explore targets beyond the $GABA_A$ and NMDA receptor systems and to develop compounds in areas of unmet need outside of brain health disorders.

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 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, like our strategic collaboration with Biogen. We may also

evaluate opportunities to acquire new compounds, product candidates or products from other companies or from academic institutions if we believe such opportunities will help us achieve our goals or meet other strategic objectives.

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 sourced our existing inventory of our proprietary formulation of ZULRESSO for commercial sale from CMOs, and intend to source all of our future commercial supplies of ZULRESSO and zuranolone and other product candidates, if approved by the FDA, from CMOs.

We have long-term supply agreements with our CMOs with respect to ZULRESSO drug substance and drug product. We have an inventory of ZULRESSO drug substance and drug product in place to help mitigate any potential supply risks. All commercial supplies are intended to be manufactured applying current Good Manufacturing Practices, or cGMP.

We are working closely with our CMOs to prepare for the potential commercialization of zuranolone in the U.S., if approved, and are in the process of completing validation batches for zuranolone. We have a long-term supply agreement with our contract manufacturer for zuranolone drug product. We have established relationships with two CMOs under which the CMOs have agreed to manufacture clinical and commercial supplies of drug substance for zuranolone under master service and quality agreements. We intend to enter into long-term commercial supply agreements with our CMOs for zuranolone drug substance. We believe that, if zuranolone were approved, we will have sufficient zuranolone drug substance and drug product for potential commercial launch later this year.

We have established relationships with CMOs under which the CMOs manufacture clinical and non-clinical supplies of drug substance and drug product for SAGE-324, SAGE-718 and other product candidates on a purchase order basis under master service and quality agreements. All clinical supplies of drug substance and drug product are intended to be manufactured under cGMP. Starting materials and key intermediates to support the production of these product candidates are manufactured by other CMOs. We do not currently have arrangements in place for either long-term supply or redundant supply of drug substance or drug product for SAGE-324 or SAGE-718. We intend to put a long-term supply agreement in place at the appropriate time for drug substance and drug product for our product candidates, 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 drug substance or drug product. We also intend to improve the manufacturing process for our product candidates and manufacture clinical supplies as development progresses.

ZULRESSO, zuranolone, SAGE-324 and SAGE-718 are small molecules isolated as stable crystalline solids. We believe the syntheses of ZULRESSO, zuranolone, 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

Our first product, ZULRESSO, was made commercially available in the U.S. as a treatment for PPD in adults in June 2019. Our revenue from sales of ZULRESSO has been negatively impacted by significant barriers arising from the complex requirements for treatment and by the lasting effects of the COVID-19 pandemic. ZULRESSO is administered as a continuous infusion given over two and a half days. Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness during the ZULRESSO infusion, ZULRESSO is approved for administration only in a medically-supervised healthcare setting that has been certified under a REMS program and meets the other requirements of the REMS program, including requirements related to monitoring of the patient during the infusion. The actions required for a healthcare setting to be ready and willing to treat women with PPD are complex and time-consuming. These actions include becoming REMS-certified; achieving formulary approvals; establishing protocols for administering ZULRESSO; and securing satisfactory reimbursement. Sites must often negotiate reimbursement on a payor-by-payor basis under commercial coverage. The availability, terms and timing of coverage for ZULRESSO vary from payor to payor, both for commercially insured patients and from state Medicaid systems, and we have encountered

some states that impose significant coverage restrictions or lengthy delays on reimbursement of ZULRESSO. As a result, certain healthcare settings will not treat Medicaid patients with ZULRESSO even if they are active sites of care for ZULRESSO. These requirements have created significant barriers to treatment for women with PPD. We expect these barriers will continue to negatively impact ZULRESSO revenue growth.

These barriers were compounded by the COVID-19 pandemic and continue to be impacted by related disruptive effects on the U.S. healthcare system and other changes to the macroeconomic environment. The spread of COVID-19 in the U.S. resulted in a significant number of sites of care pausing, limiting or delaying treatment of new patients with ZULRESSO and potential new sites of care pausing site activation activities for a period of time. We believe that, at certain points during the pandemic, concerns about exposure to the virus or its variants caused a significant reduction in the number of women with PPD seeking treatment with ZULRESSO and in the number of physicians willing to prescribe it, and that difficulties in accessing treatment with ZULRESSO have since been compounded by healthcare staffing shortages and other changes to the macroeconomic environment. Given the ongoing disruption to the healthcare system in the U.S., including as a result of staffing shortages, we cannot predict for how long and to what extent ZULRESSO sales will be adversely impacted by these factors.

Our ZULRESSO commercial operations, including our account management field-based team and sales representatives, are primarily focused on geographies that have existing, active ZULRESSO treating sites. We expect that this approach to our commercial efforts will continue to substantially limit the revenue opportunity for ZULRESSO. Given the limited focus of our commercial efforts, the number of new healthcare settings that become treating sites for ZULRESSO may be very limited. We may also find that certain healthcare settings that have in the past been active treating sites may not be willing to remain infusion-ready as a result of the complex requirements related to administration of ZULRESSO and compliance with the REMS, related limitations and restrictions, or because of actual or perceived difficulties obtaining satisfactory reimbursement or limitations on reimbursement or for other reasons, including staffing shortages. Healthcare settings that are active sites may also limit capacity used for ZULRESSO infusions or continue to wait to gain more experience with the clinical profile of ZULRESSO and to secure direct experience with reimbursement prior to increasing patient intake. Sage Central, our patient support center located in Raleigh, North Carolina, continues to provide a range of patient support resources to assist women with PPD and their families in the ZULRESSO treatment journey. In addition, our commercialization infrastructure includes capabilities in medical affairs, market access, manufacturing, quality control, drug safety and pharmacovigilance, health economics and outcomes research (HEOR), and compliance.

In December 2022, we completed our submission of an NDA to the FDA seeking approval of zuranolone for the treatment of MDD and PPD. In February 2023, our NDA was accepted for filing and granted priority review by the FDA with a PDUFA target action date of August 5, 2023. Permitted pre-launch activities, including efforts focused on disease state education in MDD and PPD, scientific exchange and permitted interactions with payers, as well as pre-launch planning and launch-readiness activities for zuranolone are underway, and we are actively working on our commercialization strategy and launch-readiness activities with Biogen in the event we are successful in our efforts to gain regulatory approval of zuranolone in the U.S. for MDD and/or PPD. In anticipation of our potential commercial launch of zuranolone in the U.S., if approved, we have begun to build additional sales and marketing capabilities in the U.S. If zuranolone receives regulatory approval for the treatment of MDD and/or PPD in adults, we expect that it may be prescribed by both specialty physicians (such as psychiatrists and obstetricians/gynecologists) and primary care physicians. We also plan to leverage additional promotional strategies to provide product education to healthcare providers and patients with MDD and PPD if zuranolone is approved, and these efforts will be supplemented with disease education efforts geared towards MDD and PPD patients and providers disseminated through similar channels. These strategies include, but are not limited to, direct-to-patient and direct-to-consumer advertising delivered through a range of media, as well as online physician education.

As described above, we and Biogen have agreed as part of our collaboration that, if zuranolone and SAGE-324 are successfully developed and approved, we will jointly commercialize the products in the U.S., including sharing equally in sales and marketing activities and profits and losses in the U.S. If we obtain regulatory approval of such products, Biogen will record sales of Licensed 217 Products and we will record sales of Licensed 324 Products. We have granted Biogen sole rights to commercialize the Licensed Products outside the U.S., other than in the Shionogi Territory with respect to zuranolone, where we have granted such rights to Shionogi.

Licenses

We have entered into several material license agreements with respect to our product and clinical-stage product candidates, which are described below.

CyDex Pharmaceuticals

In September 2015, we amended and restated our existing commercial license agreement with CyDex Pharmaceuticals, Inc., a wholly owned subsidiary of Ligand Pharmaceuticals Incorporated, 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 and the Company's compound known as SAGE-689, and the development and commercialization of the resulting products 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.

Pursuant to and during the term of the CyDex license, we are required 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 pay royalties to CyDex on sales of ZULRESSO, and will also be required to pay royalties on sales of 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 PPD. The rights licensed to us are not sublicensable.

This agreement required us to make up to $0.1 million in milestone payments in connection with the first derived product that met the relevant milestones, all of which we have already paid. We must also pay royalties of less than 1% to the Regents on ZULRESSO and for each other derived product, if any, 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 made annual maintenance fees of $15,000 until the calendar year following the first sale of ZULRESSO. 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. We pay royalties to the Regents at a low single digit percentage of net sales of ZULRESSO, 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 and License Agreement with Biogen

In November 2020, we entered into the Biogen Collaboration Agreement with Biogen for the development, manufacture and commercialization of Licensed 217 Products and Licensed 324 Products, which became effective in December 2020.

We and Biogen have agreed that we will jointly develop and commercialize the Licensed Products in the U.S., and that Biogen solely will develop and commercialize the Licensed Products outside the U.S., except, with respect to the Licensed 217 Products, in the Shionogi Territory. Each of we and Biogen is obligated to use commercially reasonable efforts to develop at least one product in each Product Class in the U.S., and Biogen is also obligated to use commercially reasonable efforts to develop at least one product in each Product Class in the Biogen Territory. We and Biogen have agreed to share jointly in the performance of the activities under the Biogen Collaboration Agreement in the U.S. and to share all costs for activities under the Biogen Collaboration Agreement solely for the U.S. equally. The Biogen Collaboration Agreement provides that Biogen has sole responsibility and decision-making authority with respect to such activities in the Biogen Territory. Biogen is solely responsible for all costs for activities under the Biogen Collaboration Agreement in the Biogen Territory. We have an Opt-Out Right (as defined below) in the U.S. with respect to a Product Class.

We have granted to Biogen a non-transferable, sublicensable, except for certain specified exceptions, license to certain of our intellectual property as needed to perform the activities under the Biogen Collaboration Agreement. Such license is co-exclusive with us in the U.S. and exclusive, even as to us, in the Biogen Territory, subject to certain retained rights to allow us to exercise our rights and perform our obligations under the Agreement and with respect to the Shionogi Territory.

Our activities for the U.S. are conducted pursuant to joint development plans agreed to by us and Biogen, on a Licensed Product-by-Licensed Product basis, and overseen by a joint steering committee, or the JSC. The JSC is composed of an equal number of representatives from each of us and Biogen.

Under the terms of the Biogen Collaboration Agreement, Biogen paid us an upfront payment of $875.0 million on December 31, 2020. For so long as a Licensed Product is being sold in the U.S., we and Biogen will share in all operating profits and losses arising from such Licensed Product in the U.S. (50 percent us and 50 percent Biogen). The Biogen Collaboration Agreement provides that Biogen will record sales of Licensed 217 Products globally. We will record sales of Licensed 324 Products in the U.S. and Biogen will record sales of Licensed 324 Products outside of the U.S., in each case if Licensed Products are successfully developed and approved. We have the right to opt out of such profit- and loss-sharing on a Product Class-by-Product Class basis in the U.S., or in each case, an Opt-Out Right. If we elect to exercise our Opt-Out Right with respect to a Product Class, we have agreed to transition to Biogen applicable development and commercial activities for such Product Class for the U.S., and Biogen has agreed to assume sole operational and financial responsibility for such activities.

The Biogen Collaboration Agreement provides for aggregate regulatory/commercial milestone payments from Biogen to us for (i) Licensed 217 Products of up to $475.0 million, including milestones totaling $225.0 million related to the first commercial sale of zuranolone in MDD and PPD in the U.S., if approved, and (ii) Licensed 324 Products of up to $520.0 million. It also provides for aggregate one-time sales milestone payments from Biogen to us of (i) up to $300.0 million for each Product Class if we have not exercised our Opt-Out Right with respect to such Product Class and (ii) up to $525.0 million for each Product Class if we have exercised our Opt-Out Right with respect to such Product Class.

Biogen has also agreed to pay us tiered royalties based on net sales of the Licensed Products in the Biogen Territory of high-teens to low-twenties percentages. If we have exercised our Opt-Out Right in the U.S. with respect to a Product Class, Biogen has agreed to pay us specified royalties based on net sales of the Licensed Products of such Product Class. Royalty payments may be reduced in certain specified customary circumstances. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may never receive any milestone payments or any royalty payments from Biogen.

During the term of the Biogen Collaboration Agreement, neither us nor Biogen nor any of our respective affiliates is permitted outside of the Biogen Collaboration Agreement to directly or indirectly develop, manufacture, conduct medical affairs activities or commercialize certain products in specified indications, or enter into agreements or arrangements with third parties to perform any of the above activities.

Unless earlier terminated, the Biogen Collaboration Agreement expires on a Licensed Product-by-Licensed Product and country-by-country basis on the later of (i) in the Biogen Territory, the expiration of the royalty term for such Licensed Product in such country or (ii) in the U.S., until the parties agree to permanently stop commercializing such Licensed Product. Biogen may terminate the Biogen Collaboration Agreement for convenience in its entirety or on a Product Class-by-Product Class basis or as to a region by providing advance written notice. Either us or Biogen may terminate the Biogen Collaboration Agreement (i) in the event of a material breach in whole or in part, by the other party subject to a cure period and (ii) in the event of the insolvency of the other party, in each case subject to specified conditions.

In connection with the execution of the Biogen Collaboration Agreement, we and BIMA also entered into a stock purchase agreement, or the Biogen Stock Purchase Agreement, for the sale and issuance of 6,241,473 shares of our common stock, or the Biogen Shares, to BIMA at a price of approximately $104.14 per share, a premium of 40% over the volume-weighted average share price for the 30 days ending on the day prior to entry into the Biogen Stock Purchase Agreement, for an aggregate purchase price of $650.0 million. The sale of the Biogen Shares was consummated on December 31, 2020.

We have granted BIMA specified demand and piggyback registration rights with respect to the Biogen Shares. The Biogen Stock Purchase Agreement also includes standstill provisions, lock-up restrictions and a voting agreement with respect to the Biogen Shares. Pursuant to the terms of the Biogen Stock Purchase Agreement, BIMA has agreed not to, and to cause its affiliates not to, directly or indirectly acquire our securities, seek or propose a tender or exchange offer or merger between us and BIMA, solicit proxies or consents with respect to any matter, or undertake other specified actions, in each case subject to specified conditions. The standstill restrictions terminate on the earliest of (i) a specified regulatory milestone under the Biogen Collaboration Agreement, (ii) the date one year following the termination of the Biogen Collaboration Agreement and (iii) December 28, 2027.

BIMA also agreed not to, and to cause its affiliates not to, sell or transfer any of the Biogen Shares for a period of eighteen months from the closing of the sale of the Biogen Shares, which period expired on June 30, 2022, and to limit sales and transfers of the Shares for an additional eighteen-month period, in each case subject to specified conditions and exceptions.

Collaboration Agreement with Shionogi & Co., Ltd.

In June 2018, we entered into a collaboration agreement with Shionogi. Pursuant to this agreement, Shionogi is responsible for all clinical development, regulatory filings and commercialization of products containing zuranolone for the treatment of MDD and potentially other indications in the Shionogi Territory. 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 zuranolone in the Shionogi Territory, 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 zuranolone in Japan. As between us and Shionogi, we maintain exclusive rights to develop and commercialize zuranolone outside of the Shionogi Territory. The upfront cash payment and any payments for milestones and royalties are non-refundable and non-creditable.

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 the Shionogi Territory for such licensed product and will ultimately expire upon the expiration of the last-to-expire royalty term. 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. 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 generally 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 and continuing technological innovation and may pursue in-licensing opportunities to develop and maintain our proprietary position. We seek to obtain domestic and international patent protection, and endeavor to promptly file patent applications for new commercially valuable inventions.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and patent scope can be reinterpreted by the courts after issuance. Moreover, many jurisdictions, including the U.S., 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 U.S. 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 U.S. 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 U.S., and in certain foreign countries. Our intellectual property holdings include, but are not limited to:

- One issued U.S. patent, exclusively licensed to us, covering a method of using our proprietary brexanolone formulation to treat PPD, which will expire in 2033; one U.S. issued patent and one granted patent in Europe covering our proprietary formulation of brexanolone, which will expire in 2033; and one U.S. issued patent covering the dosage regimen of brexanolone to treat PPD, which will expire in 2037;
- Pending U.S. and foreign patent applications covering certain aspects of brexanolone, including courses of treatment, dosage regimens, methods for manufacturing, and additional uses of the formulation of brexanolone to treat various brain health diseases and disorders, including PPD;
- One issued U.S. patent covering the composition of matter of zuranolone, three issued U.S. patents covering methods of using zuranolone, one granted European patent covering the composition of matter of zuranolone, and one granted European patent covering methods of using zuranolone, each of which expires in April 2034, subject to any potential extensions; one issued U.S. patent covering solid forms of zuranolone, which expires in August 2037, subject to any potential extensions; and pending U.S. and foreign patent applications covering zuranolone, uses of zuranolone to treat various brain health diseases and disorders, and solid forms of zuranolone;
- Issued patents covering the composition of matter for SAGE-324 in Europe and Japan, expiring in May 2035, and U.S. and foreign patent applications covering SAGE-324, SAGE-319, and many other modulators of the $GABA_A$ receptor and uses of these compounds to treat various brain health diseases and disorders;
- Two issued U.S. patents covering composition of matter and method of use of SAGE-689 which expire in December 2033, and U.S. and foreign patent applications covering SAGE-689 and uses of SAGE-689 to treat various brain health diseases and 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; and
- U.S. 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 brain health diseases and 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, and, where feasible, with consultants, scientific advisors, contractors and certain other entities with whom we do business. These agreements generally 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, designed 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 or product candidates or address similar markets. It is probable that the number of companies seeking to develop products and therapies similar to our products or targeting similar indications will increase.

Currently, there are no pharmacological therapies specifically approved for the treatment of PPD other than ZULRESSO. Current standard of care for PPD commonly consists of psychotherapy; however, patients with moderate or severe PPD are often prescribed antidepressant medications such as SSRIs and SNRIs.

Our most advanced product candidate is zuranolone, for which we filed an NDA with the FDA seeking approval for the treatment of MDD and PPD. Patients with MDD are typically treated with a variety of antidepressant medications, including SSRIs, SNRIs and atypical antipsychotics. If approved, zuranolone may also face competition for the treatment of MDD from AXS-05, a combination formulation of an NMDA receptor antagonist, dextromethorphan, with bupropion, an FDA-approved antidepressant affecting norepinephrine and dopamine, which such combination formulation was approved in August 2022 by the FDA for the treatment of MDD in adults. Zuranolone, if approved, may also face competition from esketamine, which is approved for the treatment of treatment-resistant depression and depressive symptoms in adults with MDD with acute suicidal ideation or behavior, and from cariprazine, which was recently approved for the adjunctive treatment of MDD in patients who are receiving ongoing antidepressant therapy. A number of other companies are developing product candidates intended for the treatment of MDD. Furthermore, if zuranolone is successfully approved for PPD and commercialized, it could further limit our commercial opportunity for ZULRESSO.

In the field of neuroactive steroids focused specifically on modulation of $GABA_A$ receptors, we also face competition from a number of companies, including Marinus Pharmaceuticals, Inc., or Marinus. In March 2022, Marinus announced that the FDA had approved ganaxolone, a known $GABA_A$ positive allosteric modulator neuroactive steroid, to treat seizures associated with CDKL5 deficiency disorder, a rare, genetic epilepsy. Other $GABA_A$ competitors include darigabat, which is being developed by Cerevel Therapeutics, Inc. for the treatment of epilepsy and panic disorder.

SAGE-324, a novel $GABA_A$ receptor positive allosteric modulator, is in Phase 2 development for essential tremor. If successfully developed and approved as a treatment for essential tremor, SAGE-324 will face competition from current first-line treatments which include β-adrenergic blocker propranolol and anticonvulsant primidone. Other companies are also developing potential treatments for essential tremor, including a T-type calcium channel modulator that Jazz

Pharmaceuticals, Inc. is currently evaluating in Phase 2b development and a Phase 2 T-type calcium channel modulator being developed by Praxis.

A number of companies are working to develop products designed to modulate the NMDA receptor. Aptinyx Inc. has two Phase 2 NMDA receptor modulators in development for multiple indications, targeting two indications each, including NYX-458 being developed for the treatment of cognitive impairment in Parkinson's disease. Novartis AG, following its acquisition of Cadent Therapeutics, Inc., is also developing its own NMDA receptor positive allosteric modulator, CAD-9303, which is currently being investigated in cognitive impairment associated with schizophrenia. In addition, Vaccinex, Inc. is evaluating VX15/2503, a monoclonal antibody against the protein semaphorin 4D (SEMA4D), as a treatment for cognitive impairment in Huntington's disease. Several companies have developed or are developing products for the treatment of Alzheimer's disease.

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. 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 perceived to be 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 U.S. 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 U.S., 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 delay or 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 U.S. The process required by the FDA before a drug may be marketed in the U.S. 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;
- Determination by the FDA within 60 days of its receipt of an NDA to accept and file the NDA for review;
- 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 and scheduling by the DEA, if applicable, prior to any commercial marketing or sale of the drug in the U.S.

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. These studies are typically referred to as IND-enabling studies.

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 generally involves the administration of the drug candidate to healthy volunteers and then 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 establish standards for conducting, recording data from, and reporting the results of, clinical trials, and are

intended to assure that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study participants are protected. GCPs 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 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. Companies sponsoring the clinical trials, investigators, and IRBs also must comply with, as applicable, regulations and guidelines for obtaining informed consent from the study patients, following the protocol and investigational plan, adequately monitoring the clinical trial, and timely reporting of adverse events. 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 U.S. may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. Foreign studies conducted under an IND must meet the same requirements that apply to studies being conducted in the U.S. 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 the 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 patients afflicted with the target disease 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 afflicted with the target disease 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, the 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. If concerns arise about the safety of the product candidate, the FDA or other regulatory authorities can stop clinical trials by placing them on a “clinical hold” pending receipt of additional data, which can result in a delay or termination of a clinical development program. The sponsoring

company, the FDA, or the IRB may suspend or terminate a clinical trial at any time on various grounds, including a finding that the 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.

In December 2022, with the passage of Food and Drug Omnibus Reform Act, or FDORA, Congress required sponsors to develop and submit a diversity action plan for each Phase 3 clinical trial or any other "pivotal study" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, actions plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans.

Sponsors of clinical trials are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the U.S. National Institutes of Health, or NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. The failure to submit clinical trial information to clinicaltrials.gov, as required, is a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues. Although the FDA has historically not enforced these reporting requirements due to HHS's long delay in issuing final implementing regulations, those regulations have now been issued and the FDA has issued several Notices of Noncompliance to manufacturers since April 2021.

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 U.S.

In addition, under the Pediatric Research Equity Act 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, 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 PDUFA, 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, 2023, the user fee for an application requiring clinical data, such as an NDA, is approximately $3.24 million. PDUFA also imposes an annual prescription drug program fee for human drugs of approximately $0.4 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 target action 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. With passage of FDORA, Congress clarified the FDA's authority to conduct inspections by expressly permitting inspection of facilities involved in the preparation, conduct, or analysis of clinical and non-clinical studies submitted to the FDA as well as other persons holding study records or involved in the study process.

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. 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.

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 U.S., 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 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 required 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. As part of the REMS, administration of ZULRESSO is limited to healthcare settings that have been certified under a REMS program under the supervision of qualified staff, and patients who are prescribed ZULRESSO are required to enroll in a patient registry which may allow us to compile additional information to further our understanding of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness during administration of ZULRESSO 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 if problems occur following launch, or if the FDA determines that the product is no longer safe or effective.

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 U.S., or more than 200,000 individuals in the U.S., but for which there is no reasonable expectation that the cost of developing and making a drug product available in the U.S. for this type of disease or condition will be recovered from sales of the product. If orphan product designation is sought, it must be requested before submitting an NDA for the drug for the proposed rare disease or condition. If 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 entire rare disease or condition for which the drug has been granted orphan drug designation 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.

In September 2021, the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of market exclusivity, the term "same disease or condition" in the statute means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved.

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, if approved, would provide 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, if approved, would offer 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 for 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, if approved, would provide 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.

With passage of FDORA, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded, require a sponsor of a product granted accelerated approval to submit progress reports on its post-approval studies to the FDA every six months (until the study is completed) and use expedited procedures to withdraw accelerated approval of an NDA or biologics license application, or BLA, if the confirmatory trial fails to verify the product's clinical benefit. Further, FDORA requires the agency to publish on its website "the rationale for why a post-approval study is not appropriate or necessary" whenever it decides not to require such a study upon granting accelerated approval.

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, 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 the 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. The 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. The FDA may send a Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required and have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation.

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. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug product.

Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. Further, with passage of the Pre-Approval Information Exchange Act, or PIE Act, in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. Previously, such communications were permitted under FDA guidance but the new legislation explicitly provides protection to sponsors who convey certain information about approved products or products in development to payors, including unapproved uses of approved products.

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 and the Drug Supply Chain Security Act.

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. The PREVENT Pandemics Act, which was enacted in December 2022, clarifies that foreign drug manufacturing establishments are subject to registration and listing requirements even if a drug or biologic undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the United States prior to being imported or offered for import into the United States.

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 U.S., the Department of Health and Human Services; the U.S. 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 U.S., a drug product approved by the FDA may also be subject to regulation under the 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 DEA receives notice from HHS that the FDA has approved 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 the FDA. The FDA recommended, and the DEA adopted, that brexanolone be scheduled as a Schedule IV controlled substance.

In the U.S., arrangements and interactions with health care professionals, third-party payors, patients and others 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 approved product and any future products that may 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 may be punishable by up to ten years in prison, criminal fines, damages, administrative civil money penalties, and the potential for 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 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 data breach notification laws, state health information and/or genetic privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act and the California Consumer Privacy Act), 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 or our collaborators may obtain health information from third parties, such as hospitals, healthcare professionals, and research institutions, that are subject to privacy and security requirements under the federal Health Insurance Portability and Accountability Act of 1996, and its implementing regulations, or collectively, HIPAA. HIPAA imposes privacy and security obligations on covered entity health care providers, health plans, and health care clearinghouses, as well as their "business associates" – independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service for or on behalf of a covered entity. 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, use 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 & Medicaid Services, or 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. Applicable manufacturers also are 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 payor. 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, and its implementing regulations (collectively referred to herein as the ACA (addressed further below in the section on "U.S. Healthcare Reform")). If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. Many states impose various requirements on pharmaceutical manufacturers to report development costs and pricing information when prices are increased. Penalties for late or faulty reporting can be significant. 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 CSA 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, issuance of warning or untitled letters, 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. Federal regulators, state attorneys general, and plaintiffs' attorneys have been and will likely continue to be active in this space. 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.

Many of these laws differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Many of the state laws enable a state attorney general to bring actions and provide private rights of action to consumers as enforcement mechanisms. There is also heightened sensitivity around certain types of health information, such as sensitive condition information or the health information of minors, which may be subject to additional protections. Compliance with these laws is difficult, constantly evolving, and time consuming. 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, or the testing phase, plus the time between the submission date of an NDA and the approval of that application, or the 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. 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.

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 U.S. to the first applicant to obtain approval of an NDA for a new chemical entity, or NCE. 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. We have obtained five-year NCE exclusivity for brexanolone, and plan to seek NCE exclusivity for our current and future product candidates, if eligible.

European Union Drug Development

In the European Economic Area, or EEA, our future products may also be subject to extensive regulatory requirements. As in the U.S., medicinal products can only be marketed if a marketing authorization from the competent regulatory authorities in the EU has been obtained.

Similar to the U.S., the various phases of non-clinical and clinical research in the EU are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC, or the Clinical Trials Directive, 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. Under the regime of the Clinical Trials Directive, 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 regime of the Clinical Trials Directive, 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 order to streamline the regulation of clinical trials across the EU, the EU Parliament has adopted Regulation (EU) No 536/2014, or the EU Clinical Trials Regulation. The EU Clinical Trials Regulation, which repeals and replaces the 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 main characteristics of the regulation include: a streamlined application procedure through a single entry point, referred to as the "EU portal"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts.

The EU Clinical Trials Regulation became effective on January 31, 2022 and is applicable directly in all countries of the EEA (which is comprised of 27 Member States of the EU plus Norway, Iceland and Liechtenstein). The EU Clinical Trials Regulation allows for starting and conducting a clinical trial in accordance with the Clinical Trials Directive during a transitional period which ended on January 31, 2023. Clinical trials authorized under the Clinical Trials Directive before January 31, 2023 can continue to be conducted under the Clinical Trials Directive until January 31, 2025. Any application to transition ongoing trials from the Clinical Trials Directive to the new EU Clinical Trials Regulation will need to be submitted and authorized before the end of the transitional period. The EU Clinical Trials Regulation is intended to simplify and streamline the approval of clinical trials in the EEA.

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 some EU countries, we may also be required to have an approved PIP before we can begin enrolling pediatric patients in a clinical trial.

European Union Drug Review and Approval and Post-marketing Requirements

In the EEA (which is comprised of 27 Member States of the EU plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after a related marketing authorization 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 (if marketing authorization is sought for a single EU Member State). The centralized procedure allows a company to submit a single application to the 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 countries (Iceland, Liechtenstein and Norway), all of whom make up the EEA.

The UK withdrew from the EU on January 31, 2020, commonly referred to as Brexit. Marketing authorizations granted through the EU centralized procedure continue to be valid in Northern Ireland by virtue of the Northern Ireland Protocol, but such EU marketing authorizations are not valid in the rest of the UK (England, Wales and Scotland, or collectively Great Britain). EU marketing authorizations existing as at the end of the Brexit transition period on December 31, 2020 were automatically converted into Great Britain marketing authorizations as of January 1, 2021. Until the end of 2023, a marketing authorization for Great Britain can be applied for on an expedited timetable through the UK European Commission Decision Reliance Procedure, after having received a positive opinion from the EMA's Committee for Medicinal Products for Human Use. It is not yet known whether the UK European Commission Decision Reliance Procedure will remain available after 2023. A Great Britain marketing authorization can alternatively be applied for separately through the standard national level procedure.

The EU 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 HIV, AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions 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 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, and import of medicinal products into the EU requires a manufacturing authorization allowing for import. 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 active pharmaceutical ingredients, or 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 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 and/or manufacturing authorization holders and/or distribution 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 and other healthcare professionals, misleading and comparative advertising and unfair commercial practices. For example, applicable laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities in connection with a marketing authorization approval. The SmPC is the document that provides information to physicians concerning the safe and effective use of the product. Promotional activity that does not comply with the SmPC is considered off-label and is prohibited in the EU. Breaches of the rules governing the promotion of medicinal products in the EU could be penalized by civil, criminal or administrative sanctions, which may include 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 Regulatory Data Exclusivity

In the EU, 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 qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. The concept of global marketing authorization prevents the same marketing authorization holder or members of the same group, or companies that have concluded tacit or explicit agreements concerning the marketing of the same medicinal product, from obtaining separate data and market exclusivity periods for medicinal products that contain the same active substance. This data exclusivity, if granted, prevents regulatory authorities in the EU 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 EU, 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 EU and in relation to which there exists no satisfactory method of diagnosis, prevention, or treatment (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 EU 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. 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 is established that the criteria for orphan designation are no longer met, such as 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.

European Union Data Protection

EU Member States and other jurisdictions where we may in the future operate have adopted data protection laws and regulations, which impose significant compliance obligations. For example, the General Data Protection Regulation, or GDPR, imposes strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the information provided to the individuals, the sharing of personal data with third parties, the transfer of personal data out of the EU, security breach notifications, security and confidentiality of the personal data and imposition of substantial potential fines for violations of the data protection obligations. Obligations also include the need to conclude arrangements with clinical trials sites concerning data processing activities. Data protection authorities from the different EU Member States may interpret the GDPR and applicable related national laws differently and impose requirements additional to those provided in the GDPR. In addition, guidance on implementation and compliance practices may be updated or otherwise revised, which adds to the complexity of processing personal data in the EEA.

In addition, the GDPR restricts the ability of companies to transfer personal data from the EEA to the U.S. and other countries, which may adversely affect our ability to transfer personal data or otherwise may cause us to incur significant costs to come into compliance with applicable data transfer impact assessments and implementation of legal data transfer mechanisms. One mechanism previously relied upon by U.S. companies for such transfers was the EU-U.S. Privacy Shield Framework, or Privacy Shield. However, in July 2020, the European Court of Justice ruled the Privacy Shield to be an invalid data transfer mechanism and confirmed that the European Commission's Standard Contractual Clauses, or the Model Clauses, remain valid. In June 2021, the European Commission published updated versions of the Model Clauses, which must be incorporated into new and existing agreements within prescribed timeframes in order to continue to lawfully transfer personal data outside of the EU. As a result, companies may no longer rely on the Privacy Shield as a basis on which to transfer personal data from the EU to the U.S. U.S.-based companies are permitted to rely on other authorized means and procedures to transfer personal data provided by the GDPR. The Model Clauses may also come under increased scrutiny as a result of the European Court of Justice's judgement in July 2020, though they remain the most common authorized procedure to transfer personal data out of the EU. Following the European Court of Justice's ruling, the European Data Protection Board issued a statement providing among other things that it is a primary responsibility of the exporter and the importer, when considering whether to rely on the Model Clauses to export data from the EU to third countries, to ensure that the importer maintains a level of protection that is essentially equivalent to that guaranteed by the GDPR in light of the EU Charter of Human Rights. Companies may need to revise the Model Clauses used in their contracts in light of the July 2020 judgement. Companies that have not taken steps to demonstrate that their Model Clauses and personal data recipients in the U.S. are suitable to transfer to receive the personal data may be subject to enforcement actions by competent authorities in the EU for failure to comply with related data privacy rules. In October 2022, President Biden issued an executive order to implement EU-U.S. data privacy safeguards. The European Commission is now expected to review the executive order and could propose an adequacy decision concerning the level of personal data protection in the U.S. under which personal data could flow freely from the EU to the U.S.

In addition, the privacy and data security landscape in the EU continues to remain in flux. The United Kingdom's exit from the EU, often referred to as Brexit, has created uncertainty with regard to future data protection regulation in the United Kingdom. The European Commission has adopted an adequacy decision concerning the level of data protection in the UK. Personal data may now flow freely from the EEA to the UK; however, the European Commission may suspend the adequacy decision if it decides that the UK no longer provides for an adequate level of data protection.

Rest of the World Regulation

For other countries outside of the U.S., UK 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 GCP 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 continues to remain a priority of federal and state governments, and the prices of drugs have been a focus in recent efforts. Changes in government legislation or regulation and changes in governmental health benefit programs' or commercial payors' policies governing 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. federal government and state legislatures, as well as foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and utilization management requirements, such as requirements for substitution of generic products or therapeutic equivalents. 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 state and federal healthcare reform measures. 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 was 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 has significantly impacted 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 Act's 340B drug pricing program, or 340B program, and fraud and abuse 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 Medicare 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 increased minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program and extended manufacturers' Medicaid rebate liability to drugs dispensed to individuals who are enrolled in Medicaid managed care organizations. The ACA also 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 CMS 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. Since 2022, applicable manufacturers also are 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. 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).

Some states have elected not to expand their Medicaid programs by raising the income limit to 133% of the federal poverty level for the ACA expansion population, 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 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.

Certain provisions of the ACA have been subject to judicial challenges as well as efforts to modify them or to alter their interpretation or implementation. For example, the U.S. Tax Cuts and Jobs Act of 2017, signed into law in December 2017, included 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." We expect that the ACA, its implementation, efforts to challenge or modify the ACA or its implementing regulations, or portions thereof, 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 U.S. since the ACA was enacted. For example, on August 2, 2011, the Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals for spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction, which triggered the legislation's automatic reductions. In concert with subsequent legislation, this has resulted in aggregate reductions to Medicare payments to providers of, on average, 2% per fiscal year through 2030 (with the exception of a temporary suspension from May 1, 2020 through March 31, 2022, due to the COVID-19 pandemic). On December 10, 2021, President Biden signed a law that provided for 1% Medicare sequestration in the second quarter of 2022 and the full 2% sequestration thereafter until 2030. To offset the temporary suspension during the COVID-19 pandemic, in 2030, the sequestration will be 2.25% for the first half of the year, and 3% in the second half of the year. The Infrastructure Investment and Jobs Act extended sequestration and increased it to 4% for the first six months of fiscal year 2031 before dropping to 0% for the remainder of fiscal year 2031. 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.

Further, on August 16, 2022, President Biden signed into law the Inflation Reduction Act of 2022, or IRA, which, among other things, established a Medicare Part B inflation rebate scheme, under which, generally manufacturers will owe rebates if the average sales price of a Part B drug increases faster than the pace of inflation. Failure to timely pay a Part B inflation rebate is subject to a civil monetary penalty. The IRA also establishes a Medicare Part D inflation rebate scheme, under which generally manufacturers will owe rebates if the average manufacturer price of a Part D drug increases faster than the pace of inflation. The IRA also creates a drug price negotiation program under which the prices for Medicare units of certain high Medicare spend drugs and biologics without generic or biosimilar competition will be capped by reference to, among other things, a specified non-federal average manufacturer price, starting in 2026. Failure to comply with requirements under the drug price negotiation program is subject to an excise tax and/or a civil monetary penalty. The IRA further makes several changes to the Medicare Part D benefit, including a limit on annual out-of-pocket costs, and a change in manufacturer liability under the program that could negatively affect the profitability of our product candidates, if successfully developed and approved. Congress continues to examine various policy proposals that may result in pressure on the prices of prescription drugs in the government health benefit programs. The IRA or other legislative change could impact the market conditions for our product candidates.

Additional legislative changes, regulatory changes, or guidance could be adopted, which may impact potential marketing approvals and reimbursement for our product candidates, if approved. For example, there has been increasing legislative, regulatory, and enforcement interest in the U.S. with respect to drug pricing practices. There have been several Congressional inquiries and proposed and enacted federal and state legislation and regulatory initiatives designed to, among other things, bring more transparency to product pricing, evaluate the relationship between pricing and

manufacturer patient programs, and reform government healthcare program reimbursement methodologies for drug products. Individual states in the U.S. have also increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including by requiring pharmaceutical manufacturers to report to state agencies when they introduce new drugs to market with prices over a certain threshold, or when they increase the price of a drug over a certain threshold. If healthcare policies or reforms intended to curb healthcare costs are adopted, the prices that we charge for any approved products may be limited, our commercial opportunity may be limited and/or our revenues from sales of our product and any future products, if approved, may be negatively impacted.

It is possible that the above-mentioned measures, as currently enacted or may be amended in the future, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, and new payment methodologies and additional downward pressure on coverage and payment and the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of additional cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products. We cannot be sure whether additional legislative changes will be enacted in the U.S. or outside of the U.S., or whether regulatory changes, guidance or interpretations will be changed, or what the impact of such changes on our product candidates, if any, may be.

Pharmaceutical Pricing and Reimbursement

Sales of ZULRESSO, zuranolone, if approved, and any other product candidates we successfully develop in the future depend 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 or to manage utilization by, for example, requiring prior authorization, could reduce physician usage of our products and have a material adverse effect on our sales, results of operations and financial condition. In the U.S., healthcare providers are reimbursed for covered services and products through Medicare, Medicaid, and other government healthcare programs, as well as through commercial insurance and managed healthcare organizations. No uniform policy of coverage and reimbursement for drug products exists. Further, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be set because the process for determining whether a third-party payor will provide coverage for a drug product may be separate from the process for determining the reimbursement amount for the drug product. Accordingly, decisions regarding the extent of coverage and amount of reimbursement to be provided for any of our products will each 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.

We participate in the Medicaid Drug Rebate Program and other governmental programs. The Medicaid Drug Rebate Program and other governmental programs impose obligations to report certain pricing data to the federal government as well as other compliance obligations. Other programs impose limits on the price we are permitted to charge certain entities for our products. 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 our products for which we receive regulatory approval and could negatively impact our results of operations or expand our rebate liability. For example, effective in April 2022, Congress expanded the availability of postpartum coverage under Medicaid and the Children's Health Insurance Program (CHIP).

Under the Medicaid Drug Rebate Program, we are 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 available for our drugs under Medicaid and Medicare Part B. Those rebates are based on pricing data we report on a monthly and quarterly basis to CMS, the federal agency that administers the Medicare and Medicaid programs. These data 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 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. Where our average manufacturer price increases faster than the pace of inflation, we may be subject to an additional rebate in the amount that our average manufacturer price has exceeded the pace of inflation. Currently, the rebate is capped at 100 percent of the average manufacturer price, but, effective January 1, 2024, this cap on the rebate will be removed, and our rebate liability could increase accordingly.

The ACA (addressed further above in the section on "U.S. Healthcare Reform") 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. On December 31, 2020, CMS issued a final regulation that modified prior Medicaid Drug Rebate Program regulations to permit reporting multiple best price figures with regard to value-based purchasing arrangements (beginning in 2022); and provide definitions for "line extension," "new formulation," and related terms, with the practical effect of expanding the scope of drugs considered to be line extensions that are subject to an alternative rebate formula (beginning in 2022). Our failure to comply with these price reporting and rebate payment options, as well as pharmaceutical benefit manager "accumulator" programs, could negatively impact our financial results.

Federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the 340B drug pricing program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B 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 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 are found to have knowingly and intentionally overcharged covered entities, which became effective on January 1, 2019. It is unclear how HRSA will apply its enforcement authority under the regulation. We also are required to report our 340B ceiling prices to HRSA on a quarterly basis, and HRSA then publishes them to covered entities. Moreover, under a final regulation effective January 13, 2021, HRSA newly established an administrative dispute resolution, or ADR, process for claims by covered entities that a manufacturer has engaged in overcharging, and by manufacturers that a covered entity violated the prohibitions against diversion or duplicate discounts. Such claims are to be resolved through an ADR panel of government officials rendering a decision that could be appealed only in federal court. HRSA has recently issued a proposed rule to modify the ADR process, which could impact the procedures that are used to determine whether we owe additional 340B discounts. An ADR proceeding could subject a manufacturer to onerous procedural requirements and result in additional liability.

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. Starting in 2023, manufacturers must pay refunds to Medicare for single source drugs or biologics, or biosimilar

biological products, reimbursed under Medicare Part B and packaged in single-dose containers or single-use packages, for units of discarded drug reimbursed by Medicare Part B in excess of 10 percent of total allowed charges under Medicare Part B for that drug. Manufacturers that fail to pay refunds could be subject to civil monetary penalties of 125 percent of the refund amount.

Statutory or regulatory changes or CMS guidance could affect the average sales price calculations for our approved 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 legislation enacted by Congress.

Congress also could enact additional changes that affect our overall rebate liability and the information we report to the government as part of price reporting calculations, which could impact the market conditions for our products. We further expect continued scrutiny on government price reporting and pricing more generally from Congress, agencies, and other bodies, and are seeing an increase in state interest in price reporting, transparency, and other policies to address drug pricing concerns.

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 become aware that our Medicaid reporting for a prior period 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 three years from the period 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 covered entities under the 340B program, and may require us to issue refunds to 340B covered entities, which can be costly and burdensome.

Further, the IRA establishes Medicare Part B and Part D inflation rebate schemes (the first Part B inflation rebate period is in first quarter 2023; the first Part D inflation rebate period is in fourth quarter 2022 through third quarter 2023) and a drug price negotiation program, with the first negotiated prices to take effect in 2026. It also makes several changes to the Medicare Part D benefit, including the creation of a new manufacturer discount program in place of the current coverage gap discount program (beginning in 2025). Manufacturers may be subject to civil monetary penalties for certain violations of the negotiation and inflation rebate provisions and an excise tax during a noncompliance period under the negotiation program. Drug manufacturers may also be subject to civil monetary penalties with respect to their compliance with the new Part D manufacturer drug discount 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 for each misrepresentation and for each day in which the misrepresentation was applied, 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, or to have misrepresented that information, 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 failures also could be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we participate in the Medicaid program, or, if we fail to comply with 340B program requirements, HRSA could decide to terminate our 340B program participation agreement. In the event that CMS terminates our rebate agreement or HRSA terminates our 340B program participation agreement, no federal payments would be available under Medicaid or Medicare Part B for our covered outpatient drugs.

CMS and the Office of Inspector General 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. We cannot guarantee 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 (collectively, the Big Four agencies) and certain federal grantees, we are 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 are 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, 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 are 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, requires 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 U.S., 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 presented a proposal for a regulation on health technologies assessment. The proposal was adopted in December 2021 and will apply as of January 2025. This EU HTA Regulation 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.

Employees and Human Capital

Our mission to pioneer solutions to deliver life-changing brain health medicines so every person can thrive depends on our ability to attract, develop, engage, and retain the industry's highest quality talent across all dimensions of diversity. This understanding guides our approach to recruiting, managing and supporting our human capital resources. At Sage, we strive for a best-in-class working culture and a spirit of collaboration and inclusivity with a goal of supporting our team members and their families while we work to achieve our mission and evolve our business and culture as we grow. At Sage, we believe every voice matters and every contribution counts.

General Information. As of February 8, 2023, we employed 689 full-time employees, including 360 in research and development and 329 in selling, general and administrative and no part-time employees. Approximately 33 of our employees hold M.D. or Ph.D. degrees. We have never had a work stoppage, and none of our employees are represented by a labor organization or under any collective-bargaining arrangements. We consider our employee relations to be good.

Diversity, equity, and inclusion

We are committed to taking action to integrate diversity, equity, inclusion, and equal opportunity to foster a diverse workforce, sense of belonging and innovative thinking. We have four core areas of focus:

- **Experience:** Foster a diverse and inclusive culture that enables a sense of belonging and innovative thinking.
- **Talent:** Recruit and develop diverse, high-performing individuals and teams.
- **External:** Identify and partner with diverse community organizations and vendors to increase diversity in our ecosystem.
- **Patients:** Continue to grow and nurture long-term and transparent relationships to ensure diverse voices are represented.

Our commitment to diversity, equity, and inclusion is a core focus of our leadership team: nine of our seventeen leadership team members are women and/or from diverse racial and ethnic groups. As of year-end 2022, approximately 63% of our U.S. workforce identified as female and 30% identified as racially or ethnically diverse.

Compensation, Benefits and Ongoing Professional Development

Our vision is to fearlessly lead the way to create a world with better brain health, which requires everyone to consistently give their best. We aim to spur every single employee on to realize their true potential. To do this, we appreciate what it takes to be at one's best, which is why we prioritize the health and well-being of all team members. To promote our employees' continued well-being and development, we offer a variety of inclusive benefits and opportunities. We offer comprehensive work-life and income protection benefits, including health, dental, vision, life insurance, disability and retirement savings programs, paid time off and family leave, family planning, mental health days, caregiving support, a "be well" subsidy, technology benefits, tuition reimbursement and an employee assistance program. We continue to prioritize the needs of our employees through a robust listening strategy and are focused on assessing and responding to evolving needs.

Our employees are encouraged to take advantage of an array of professional and career development resources delivered through a variety of venues, including continued learning courses, online learning, company-wide coaching, podcasts, and leadership circles. We believe our investment in learning and growth gives us a competitive edge and our strategies are focused on optimal performance, ongoing professional growth, and future of work capabilities, with the following areas of focus:

- **Critical Leadership Capabilities**: Build a culture where leaders drive inclusion, performance, curiosity, and personal and professional growth.
- **Create a change agile and integrated organization**: Maximize our ability to collaborate and forge new pathways in the face of change.

- **Strengthen our commitment to personal and professional growth**: Increase engagement and retention through learning investment in individual employees.

We are committed to fostering an environment in which everyone feels valued, respected, and empowered to contribute and provided access to the resources and opportunities to do their best work, while we strive to make a positive difference for patients and their families.

Corporate Information

We 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 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 on Form 10-K, or 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

Our future business prospects depend heavily on our ability, with our collaboration partner, Biogen, to gain regulatory approval of zuranolone (SAGE-217) in the U.S. as a treatment for major depressive disorder, or MDD, and postpartum depression, or PPD, and to successfully commercialize zuranolone in those indications, if approved. While our NDA for zuranolone is currently under review, we cannot be certain that the design and results of our development program for zuranolone will be sufficient to obtain regulatory approval of zuranolone for the treatment of MDD or PPD on the timelines we expect or at all. Even if we receive regulatory approval of zuranolone in MDD and PPD, our commercialization efforts with respect to zuranolone may not be successful.

Our future business prospects depend heavily on our ability, along with our collaboration partner, Biogen, to gain regulatory approval of zuranolone in the U.S. as a treatment for MDD and PPD.

Our NDA seeking approval of zuranolone for the treatment of both MDD and PPD was accepted for filing by the U.S. Food and Drug Administration, or FDA, and granted priority review in February 2023, with a Prescription Drug User Fee Act, as amended, or PDUFA, target action date for the NDA of August 5, 2023. The FDA may not approve zuranolone as a treatment for MDD and/or PPD on the timelines we expect, or at all. The FDA may require additional trials or data to approve zuranolone as a treatment for MDD and/or PPD, any of which may significantly delay and put at risk our efforts to obtain approval and may not be successful. The FDA may determine that the manufacturing processes or facilities of third-party contract manufacturers with which we contract for the manufacture of zuranolone do not conform to applicable requirements, including current Good Manufacturing Practices, or cGMPs. The FDA may find deficiencies in the conduct of clinical trials or nonclinical studies or in the preparation, collection or analysis of data from clinical and non-clinical studies submitted in our NDA. If our NDA for zuranolone is reviewed by an advisory committee of the FDA, the advisory committee may recommend against approval of the 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 may also approve zuranolone, but only for one of the indications described in our NDA or for only a specific subset of patients with MDD or PPD, or may impose other restrictions, such as limitations or restrictions in the approved label such as a boxed warning, contraindications or a REMS requirement. The FDA may not meet expected review timelines or may elect to extend the timeframe for their review, or there may be delays at any point in the regulatory review cycle that negatively impact our plans and expectations, including anticipated launch timelines and plans in MDD or PPD. Other decisions or actions of the FDA or other regulatory agencies may also adversely affect the zuranolone program, our plans, progress or results and the potential product profile and success of zuranolone. Even if zuranolone is approved for marketing, it may not have the profile or market acceptance we expect in clinical practice after launch or the unmet need for new treatment options in MDD may not be as we significant as we expect or we may encounter reimbursement-related or other market-related issues in the commercialization of zuranolone. We and our collaborator may never be able to successfully commercialize zuranolone in the approved indications or to meet our expectations with respect to timing and revenues or profits from sales of such product.

Our future business prospects depend heavily on our ability, alone or through our collaborations, to successfully develop, gain regulatory approval of and commercialize our current and future product candidates beyond zuranolone. We cannot be certain that we will be able to initiate planned clinical trials, to complete ongoing clinical trials or to

announce results of such trials with respect to any of our other product candidates, on the timelines we expect or at all, or that the results of our clinical trials or other activities under our development programs will be positive. We cannot be certain that we or our collaborators will be able to advance such product candidates into additional trials or to successfully develop, obtain regulatory approval for, or successfully commercialize any of our such product candidates, if approved.

Our future business prospects depend heavily on our ability, alone or through our collaborations, to successfully develop and gain regulatory approval of our current and future product candidates beyond zuranolone. Drug development and obtaining regulatory approval for a product involves a long, expensive and uncertain process, involving a high degree of risk.

Before obtaining regulatory approvals for the commercial sale of any product candidate, non-clinical studies and clinical trials must demonstrate that the product candidate is safe and effective for use in each target indication. We or our collaborators, as applicable, may not be able to demonstrate the efficacy and safety of any of our other current product candidates or any future product candidate at each stage of clinical development or we may encounter other issues with any clinical trials or non-clinical studies required for regulatory submissions. Success in non-clinical studies or in earlier clinical trials or interim results of clinical trials may not be repeated or observed in ongoing, future or completed studies or trials involving the same compound or other product candidates. Some or all of our or our collaborators' clinical trials may fail to meet their primary or key secondary endpoints, raise safety issues or generate mixed results. For example, in December 2019, we announced that the MOUNTAIN Study, a Phase 3 clinical trial of zuranolone for the treatment of MDD, did not meet its primary endpoint. We may find that studying alternate formulations of our product candidates or doses that achieve higher or lower patient exposure may result in unexpected adverse events or raise other safety issues or may otherwise generate negative results. For example, in our ongoing dose-ranging study of SAGE-324, the KINETIC 2 Study, we are evaluating multiple doses, including the same maximum dose of SAGE-324 that we evaluated in prior studies. We might decide to evaluate different doses, formulations, and durations of dosing for any of our product candidates with other studies or programs in the future. 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 file for and obtain regulatory approval on the timelines we expect or at all. Other decisions or actions of the FDA or other regulatory agencies may affect our plans, progress or results.

Changes in formulation or the need to refine or scale-up the manufacturing process as we do for any of our product candidates could also delay development or require us to conduct additional clinical trials or non-clinical studies or conduct post-approval analyses, or could lead to different results than achieved with the earlier formulation or processes. We or our collaborators may not be able to initiate or complete our clinical trials or announce results from our clinical trials on the timelines we expect. We or our collaborators may experience slower than expected activation of sites or enrollment and randomization of patients in our clinical trials, particularly in clinical trials where an in-patient stay or frequent site visits are required, the patient population is small, enrollment criteria are more selective than historically used, there are existing therapies, where other companies are running large clinical trials, or where relevant clinical sites or our vendors are experiencing healthcare staffing shortages or significant turnover. There is also the potential for slower than expected clinical site initiation, delays or problems in analyzing data, the potential need for additional analysis or data or the need to enroll additional patients, or other unexpected issues such as adverse events in any of our clinical trials. These types of delays or issues could lead to delays in the completion of a trial and announcement of results.

Our ongoing and planned development activities may be negatively impacted by a number of factors, including the downstream effects of the COVID-19 pandemic. Widespread healthcare and vendor staffing shortages and increased competition for patients and clinical sites may make it difficult to enroll patients in our clinical trials and/or identify and activate participating clinical sites for our trials, may cause other delays at clinical trial sites and/or vendors, and may increase the rates of patients withdrawing from our clinical trials following enrollment. Some clinical sites may decline or delay participation in our trials due to capacity and resource constraints, given the increase in the number of clinical trials being conducted as pandemic-related restrictions have lifted. These factors may substantially slow clinical site identification and activation and enrollment in our clinical trials, or cause us to pause trials, which may, in each case, significantly impact our ability to meet our expected timelines, budgets, or other plans. For example, as a result of a slower than anticipated pace of enrollment, we now expect to complete enrollment in our KINETIC 2 Study of SAGE-324 in late 2023, rather than in late 2022 as we had initially projected.

In response to these challenges during the COVID-19 pandemic, we or our clinical sites implemented measures to help minimize the number of visits a clinical trial participant is required to make to a site, including by limiting or modifying clinical trial procedures and visits for data collection, and some clinical sites imposed other restrictions or limitations on key clinical trial activities such as restrictions related to monitoring of the sites by clinical research organizations. Some of these restrictions and limitations could be implemented again in the future, including in connection with the emergence of new COVID-19 strains. Limitations or modifications to study procedures, study visits or data collection, restrictions on key clinical trial activities such as monitoring or auditing, or other restrictions that may affect data analysis activities may require additional assessment and evaluation from institutional review boards; negatively impact the integrity or completeness of our trial data, the powering of a trial, the integrity or relevance of clinical study endpoints; or impact the timing of availability of results.

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. 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 current or future product candidates will be successfully developed or commercialized either in the U.S. or in any country outside the U.S. Even if we or our collaborators conduct the trials required by or discussed with the FDA, the FDA may ultimately decide that the design, number and type of trials, number of patients studied or results, even if positive, are not sufficient to file for or gain regulatory approval of any of our product candidates in the indications we study, or do not support the safety or efficacy or our intended profile for the product.

Even if we or a collaborator of ours gains approval of any of our current or future product candidates, we and our collaborator may never be able to successfully commercialize such new product in the approved indications or meet our expectations with respect to timing and revenues or profits from sales of such product.

We may never be able to generate meaningful revenues from sales of ZULRESSO® (brexanolone) CIV injection at levels or on timing necessary to support our investment and goals.

Our first product, ZULRESSO, was approved by the FDA in March 2019 as a treatment for PPD in adults, and was made commercially available in June 2019. We may never be able to generate meaningful revenues from sales of ZULRESSO or revenues at levels or on timing necessary to support our investment and goals. Our revenues from sales of ZULRESSO have been negatively impacted by significant barriers arising from the complex requirements for treatment and by the direct and indirect impacts of the COVID-19 pandemic. Some or all of these factors are expected to continue to impact revenues negatively in the future.

ZULRESSO is administered as a continuous infusion given over two and a half days. Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness during the ZULRESSO infusion, ZULRESSO is approved for administration only in a medically-supervised healthcare setting that has been certified under a Risk Evaluation and Mitigation Strategy, or REMS, program and meets the other requirements of the REMS program, including requirements related to monitoring of the patient during the infusion. The actions required for a healthcare setting to be ready and willing to treat women with PPD are complex and time-consuming. These actions include becoming REMS-certified; achieving formulary approvals; establishing protocols for administering ZULRESSO; and securing satisfactory reimbursement. Sites must often negotiate reimbursement on a payor-by-payor basis under commercial coverage. These requirements have created significant barriers to treatment for women with PPD. We expect

these barriers will continue to negatively impact ZULRESSO revenue growth, but we do not know the extent of the anticipated impact. These barriers were compounded by the COVID-19 pandemic and continue to be impacted by its related disruptive effects on the U.S. healthcare system, and other changes to the macroeconomic environment.

The spread of COVID-19 in the U.S. resulted in a significant number of sites of care pausing, limiting or delaying treatment of new patients with ZULRESSO and potential new sites of care pausing site activation activities for a period of time. We believe that, at certain points during the COVID-19 pandemic, concerns about exposure to the virus or its variants caused a significant and sustained reduction in the number of women with PPD seeking treatment with ZULRESSO and in the number of physicians willing to prescribe it, and that difficulties in accessing treatment with ZULRESSO have now been compounded by healthcare staffing shortages and other changes to the macroeconomic environment. Given the ongoing disruption to the healthcare system in the U.S., including as a result of staffing shortages, we cannot predict for how long and to what extent ZULRESSO sales will be adversely impacted by these factors.

Our commercial efforts for ZULRESSO, including our account management field-based team and sales representatives, are primarily focused on geographies that have existing, active ZULRESSO treating sites. We expect that this approach will continue to substantially limit the revenue opportunity for ZULRESSO, and may make it difficult for us to achieve revenue growth and meet our revenue goals. Given this approach, the number of new healthcare settings that become treating sites for ZULRESSO, if any, is also expected to be limited. We may also find that certain healthcare settings that have in the past been active treating sites may not be willing to remain infusion-ready as a result of the complex requirements related to administration of ZULRESSO and compliance with the REMS, related limitations and restrictions, or because of actual or perceived difficulties obtaining satisfactory reimbursement or limitations on coverage and reimbursement or for other reasons, including staffing shortages. Healthcare settings that are active treating sites may also limit capacity used for ZULRESSO infusions.

We continue to encounter other issues and challenges in commercializing ZULRESSO and generating revenues, including:

- Some women with PPD who need treatment find it too onerous to undergo an infusion or to be treated at a certified healthcare setting overnight for the length of stay required for treatment, or to be enrolled in the registry that is part of the REMS process or may be concerned about the risk of excessive sedation and sudden loss of consciousness.
- More healthcare providers than we expected have been unwilling to accept ZULRESSO as a treatment paradigm for women with PPD and this may continue; we believe this unwillingness is due primarily to the product profile and reimbursement challenges associated with ZULRESSO.
- We compete with lower cost antidepressants.
- Given the mode of administration, the nature of the REMS and the current limitation on the administration of ZULRESSO to a medically-supervised healthcare setting certified under the REMS, use of ZULRESSO in the U.S. has been focused primarily on women with more severe symptoms of PPD, and we expect that to continue.
- We may be unable to fully comply with our obligations under the ZULRESSO REMS, which include auditing of healthcare settings, collection and analysis of required data, and other requirements, to the satisfaction of the FDA, or the FDA may require modifications to or additional restrictions under the ZULRESSO REMS.
- If zuranolone is successfully approved for PPD and commercialized, it could further limit our commercial opportunity for ZULRESSO.

We also expect to continue to encounter challenges related to coverage and reimbursement of ZULRESSO. These include restrictions related to the severity of PPD cases for which ZULRESSO will be reimbursed, requirements that other treatments be used prior to ZULRESSO, or other limitations in the scope, breadth, availability or amount of reimbursement covering ZULRESSO or the infusion. For example, the availability, terms and timing of coverage for ZULRESSO by state Medicaid systems is expected to continue to vary significantly by state, and we encounter states that impose significant coverage restrictions or lengthy delays on reimbursement of ZULRESSO. Similarly, certain healthcare settings or patients may determine that the financial burdens of treatment are not acceptable. A number of healthcare

settings that are willing to administer ZULRESSO to women with PPD who have commercial insurance do not currently treat Medicaid patients, which adversely affects our ability to generate revenue from ZULRESSO.

Any of these issues could impair our ability to generate revenues or to meet our expectations with respect to the amount or timing of revenues. Any issues or hurdles related to our commercialization efforts may materially adversely affect our business, results of operations, financial condition and prospects and could lead us to make significant further changes to the scope and nature of our efforts. There is no guarantee that we will be successful in our commercialization efforts with respect to ZULRESSO, or that we will be able to generate meaningful revenues or revenues at the levels or on the timing necessary to support our investment and goals.

ZULRESSO, zuranolone, and our other current or future product candidates and any future products, if successfully developed and approved, may cause undesirable side effects that limit their commercial profile; delay or prevent further development or regulatory approval; cause regulatory authorities to require labeling statements, such as boxed warnings or a REMS; or result in other negative consequences.

We may observe undesirable side effects or other potential safety issues in nonclinical studies, in clinical trials at any stage of development of our product candidates, as part of an expanded access program, if initiated for any of our products or product candidates, in commercial use or in post-approval studies of any approved product. 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 ZULRESSO, zuranolone, any other current or future product candidates, or any future products, if successfully developed and approved, may only be uncovered with a larger number of patients exposed to the product. Those side effects could be serious or life-threatening. If we or others identify undesirable side effects caused by ZULRESSO, zuranolone, any other existing or future product candidate or any future approved product:

- regulatory authorities may withdraw, withhold or limit their approval of such products;
- the FDA or regulatory authorities outside the U.S. may impose a clinical hold or partial clinical hold prior to the initiation of development or during development of our product candidates which could cause us or our collaborators to have to stop, delay or restrict further development; or we or our collaborators may, even without a clinical hold, decide to interrupt, delay or halt existing non-clinical studies and clinical trials or stop development;
- we may have difficulty enrolling patients in our clinical trials and completing such trials on the timelines we expect or at all, or we may have to conduct additional non-clinical studies or clinical trials as part of a development program;
- if an NDA for any of our product candidates is reviewed by an advisory committee of the FDA, the advisory committee may recommend against approval of the 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;
- we or our collaborators may not be able ultimately to demonstrate, to the satisfaction of the FDA or other regulatory authorities, that our product candidates are safe and that the benefits outweigh the safety risks, and the FDA or applicable foreign regulatory authorities may not approve the product candidate;
- regulatory authorities may require the addition of labeling statements, such as a boxed warning or additions to an existing boxed warning, or a contraindication, including as a result of inclusion in a class of drugs for a particular disease, or may require a REMS, or modifications to an existing REMS;
- we or our collaborators may be required to change the way such products are distributed or administered, conduct post-approval studies or change the labeling of the products;
- we or our collaborators may be subject to regulatory investigations and government enforcement actions;
- we or our collaborators may decide to remove such products from the marketplace;
- we or our collaborators could be sued and held liable for injury caused to individuals exposed to or taking our products or 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, could substantially increase the risks and costs of developing our product candidates or commercializing our products, and could significantly adversely impact our ability and that of our collaborators to successfully develop, gain regulatory approval for, and commercialize our current product candidates or future products and generate revenues.

Obtaining regulatory approval to market any of our 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 zuranolone or any of our other product candidates for many reasons. Any setback or delay in obtaining regulatory approval for zuranolone or any of our other 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 or our collaborators receive approval of an NDA from the FDA or in any foreign countries until we or our collaborators 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. The FDA and regulatory authorities outside the U.S. may delay, limit or deny approval of zuranolone or any of our other product candidates for many reasons, including, among others:

- we or our collaborators 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 or other criteria required by the FDA or regulatory authorities outside the U.S. for marketing approval;
- the FDA or regulatory authorities outside the U.S. may impose a clinical hold or partial clinical hold prior to the initiation of development or during development of our product candidates which could cause us to have to stop, delay or restrict further development;
- 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, implementation or result of our non-clinical studies or clinical trials is inadequate for regulatory approval or that changes in dosing or 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 or our collaborators 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 of the FDA, the advisory committee may recommend against approval of the 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 or our collaborators are seeking regulatory approval for a more limited patient population than expected or with substantial use restrictions;
- as was the case with ZULRESSO, the FDA may require a REMS as a condition of approval or post-approval for our product candidates, or may modify an existing REMS;

- 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 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 or our collaborators' ability to obtain regulatory approval for and successfully market zuranolone or our other product candidates. Even if we or our collaborators receive marketing approval for zuranolone or any of our other 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, the FDA has imposed post-approval obligations in connection with approval of ZULRESSO. We may not be able to fulfill these obligations in accordance with the FDA's timelines, or at all. We expect the FDA to recommend scheduling with respect to zuranolone, and the FDA may also recommend scheduling with respect to any of our other current or future product candidates. In such event, as was the case with ZULRESSO, prior to a product launch, the U.S. Drug Enforcement Administration, 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 would delay our ability to market any product candidate that is successfully developed and approved.

We have been granted priority review of our NDA seeking approval of zuranolone for the treatment of MDD and PPD. We may seek priority review of future NDA submissions with the FDA, if our development efforts with respect to other product candidates are successful, but the FDA may not grant such priority review. Even if the FDA grants priority review for an NDA, the FDA may not meet the applicable review timelines or may elect to extend the timeframe for their review. Delays, resource constraints, and other disruptions at the FDA and other agencies may 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, the U.S. government has shut down several times in recent history and certain regulatory agencies, including the FDA, had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs in the future, 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.

Fast Track and Breakthrough Therapy designations from the FDA or PRIority Medicines, or PRIME, designation from the European Medicines Agency, or EMA, 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 COVID-19 pandemic, its related downstream effects, and changes to the macroeconomic environment have adversely impacted and may continue to adversely impact our business, including our sales of ZULRESSO and our initiation, conduct and completion of non-clinical studies and clinical trials.

The COVID-19 pandemic in the U.S. resulted in a significant number of sites of care pausing treatment of new patients with ZULRESSO and potential new sites of care pausing site activation activities for a period of time. We believe, at certain points during the pandemic, concerns about exposure to the virus or its variants caused a significant and sustained reduction in the number of women with PPD seeking treatment with ZULRESSO and in physicians willing to prescribe it, and that difficulties in accessing treatment with ZULRESSO have since been compounded by healthcare staffing shortages and other changes to the macroeconomic environment. Given the ongoing disruption to the healthcare system in the U.S., including as a result of staffing shortages, we cannot predict for how long and to what extent ZULRESSO sales will be adversely impacted by these factors.

As a result of the COVID-19 pandemic, its downstream effects, and changes to the macroeconomic environment we could observe delays or other disruptions that may negatively impact our ongoing and planned development activities, including the timing of initiation and completion of non-clinical studies and clinical trials or the integrity, completeness or usefulness of the data we collect in those studies or trials. These delays and disruptions may include:

- delays or difficulties in qualifying clinical sites and in clinical site activation, or the diversion of other healthcare resources and personnel, due to healthcare and vendor staffing shortages or as a result of recommended or required precautions or limitations that could be implemented in the future;
- delays or difficulties in enrolling patients in our clinical trials, including, for example, with respect to recruiting older patients as we saw in certain clinical trials at certain times during the pandemic, or an increase in the number of patients withdrawing from our clinical trials prior to completion as a result of concerns about potential future variants of COVID-19 or as a result of recommended or required precautions or limitations intended to curb the spread of the virus, or the potential that patients in our trials may have or contract COVID-19 or potential future variants of the virus which may impact the trial results;
- delays or disruptions in non-clinical studies due to precautions taken by contract research organizations, or CROs, or other vendors in response to potential future restrictions recommended or imposed by federal, state or local authorities;
- limitations or modifications to study procedures, the number and type of study visits or data collection or data analysis activities, or other restrictions on other key clinical trial activities such as monitoring and auditing, in response to potential variants of COVID-19 or as a result of future restrictions imposed or recommended by federal, state or local governments;
- interruption or delays in the operations of the FDA and foreign regulatory agencies, including as a result of staffing shortages or other resource constraints, which may impact timelines for initiation of clinical trials, amendments of protocols, inspections of manufacturing facilities and review of regulatory submissions;
- interruption of, or delays in, availability of supplies of our product candidates if the COVID-19 pandemic continues in surges or recurs in waves for an extended period, including the potential for shortages of raw materials, other drugs or materials used in our clinical trials, or staff available to our contract manufacturing organizations or other vendors in the supply chain or as the result of restrictions or limitations in their businesses or activities; and
- limitations on employee resources that would otherwise be focused on the conduct of our non-clinical studies and clinical trials, including due to illness as a result of potential future waves of variants of COVID-19.

Additionally, future surges of COVID-19 may cause economic disruptions and may in the future adversely impact the capital markets and make additional capital unavailable to us on acceptable terms, or at all if we were to seek it. There may also be other long-term negative effects of the COVID-19 pandemic that may negatively affect general economic conditions and adversely impact our ability to access the capital markets in the future.

The number of people with the diseases and disorders for which our products and product candidates are targeted may be smaller than we expect or our other assumptions with respect to the potential markets for our products and product candidates may not be correct and the markets may be significantly smaller than we expect.

Our first product, ZULRESSO, has been approved in the U.S. for the treatment of PPD in adults. We completed a rolling submission of an NDA to the FDA seeking approval of zuranolone for the treatment of MDD and PPD in December 2022. We are developing SAGE-324 as a potential oral therapy for neurological conditions, such as essential tremor, epilepsy and Parkinson's disease. We are developing SAGE-718 as a potential treatment for cognitive dysfunction associated with Huntington's disease, Parkinson's disease and Alzheimer's disease. 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 PPD, MDD, essential tremor and the other indications for which we are developing, or plan to develop, our product candidates, we estimate the prevalence of the disease or disorder, and our estimates as to prevalence, including the assumptions we apply in determining our estimate, may not 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 some patients being reluctant to seek treatment in clinical practice. The actual number of patients with PPD,

MDD, essential tremor, Huntington's disease, Parkinson's disease, Alzheimer's disease, or any other indication for which we elect to pursue development of our product candidates may, however, be significantly lower than we believe. Even if our prevalence estimates are correct, any approved product that we develop may only be indicated for or used by a subset of patients with the relevant disease or disorder. Our assumptions and estimates about the market for ZULRESSO and the potential market for zuranolone and our other current and future product candidates may not be accurate. In the event the number of patients with the diseases and disorders we are studying is significantly lower than we expect, we or our collaborators may have difficulties in enrolling patients in our clinical trials which may delay or prevent development of our product candidates. If our prevalence estimates with respect to any indication or our other market assumptions are not accurate, the markets for any approved product 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 the level and timing of revenues or profits.

Positive results from 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 in the same indications or other indications. Interim results from non-clinical studies and clinical trials may not be predictive of results of such non-clinical studies or clinical trials once completed. 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 in the same indications or other indications, or we cannot replicate our interim results in our completed 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 or our collaborators may obtain from subsequent non-clinical studies or clinical trials using the same product candidate or other product candidates. For example, unlike earlier trials of zuranolone in MDD and PPD, the Phase 3 MOUNTAIN Study evaluating zuranolone in patients with MDD did not meet its primary endpoint. We or our collaborators may find that ongoing or future clinical trials of zuranolone or any of our other product candidates may also fail to meet their primary endpoints. Similarly, interim results from non-clinical studies and clinical trials may not be predictive of results of a non-clinical study or clinical trial once completed.

We or our collaborators may also observe safety issues in clinical trials or non-clinical studies of our product candidates that we or they did not observe or appreciate in earlier stage clinical studies or non-clinical studies, or a different rate or severity of events, including as a result of an increase in dosing or in frequency or duration of dosing, studying a different patient population or different indication than previously studied, or administering a product candidate with a concomitant medication. For example, in our ongoing dose-ranging study of SAGE-324, we are evaluating multiple doses, including the same maximum dose of SAGE-324 that we evaluated in prior studies. Any of these studies may result in unexpected adverse events or raise other safety issues or may otherwise generate negative results.

The results from non-clinical animal models may not be replicated in clinical trials. Many product candidates, including many targeting central nervous system disorders, with promising non-clinical profiles have failed to demonstrate similar safety, non-toxicity and efficacy in humans.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later-stage clinical trials after achieving positive results in earlier-stage development, and we cannot be certain that we will not face similar setbacks. Many drugs have failed to replicate efficacy and safety results in larger or more complex later stage trials. 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 or our collaborators fail to produce positive results in our ongoing and 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, enrollment or completion of our ongoing and planned clinical trials of our current and future 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 such product candidate and to generate revenue from resulting products, if any.

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 ongoing clinical trials will be completed, and results announced, or whether future trials will begin, as planned or expected, if at all, as the commencement, enrollment 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 one or more clinical trials on full or partial clinical hold;
- delay or inability to satisfy the requirements of the FDA to commence clinical trials, including chemistry, manufacturing and control, or CMC, requirements, or to file or receive approvals of additional investigational new drug applications, or INDs, that may be required;
- delay or inability to satisfy the requirements for clinical trials conducted in the EU, if applicable, pursuant to Regulation (EU) No 536/2014, or the EU Clinical Trials Regulation;
- negative or inconclusive results from our ongoing non-clinical studies or clinical trials;
- challenges in identifying, recruiting, enrolling and retaining patients to participate in clinical trials;
- challenges in qualifying and activating clinical trial sites, including due to capacity and resource constraints and attrition at sites, and potential delays at clinical trial sites;
- the impact of the COVID-19 pandemic and its downstream effects, and/or the impact of other macroeconomic and geopolitical conditions;
- delays in reaching or failing to reach agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- inadequate quantity or quality of supplies of a product candidate or other materials necessary to conduct clinical trials;
- 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;
- 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; and
- reports from non-clinical or clinical testing of other therapies that raise safety or efficacy concerns.

In addition, a clinical trial may be suspended or terminated by us, the FDA or other regulatory authorities, the IRB or Ethics Committee, or EC, at the sites where the IRBs or ECs are overseeing a clinical trial, or recommended for termination or suspension by a data and safety monitoring board 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; and
- problems with clinical supply materials.

Additionally, changes in regulatory requirements or guidance or unanticipated events during our non-clinical studies and clinical trials may force us or our collaborators to amend non-clinical studies and clinical trial protocols or the applicable regulatory authorities may impose additional non-clinical studies and clinical trial requirements. Amendments or changes to 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. If we or our collaborators experience delays completing, or if we or our collaborators terminate, any of our non-clinical studies or clinical trials, or if we or our collaborators 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 from resulting products, if any, will be delayed.

We or our collaborators may never seek or receive regulatory approval to market any of our products or product candidates outside of the U.S., or receive pricing and reimbursement outside the U.S. at acceptable levels.

We or our collaborators may not seek, or may seek but never receive, regulatory approval to market our products or product candidates outside of the U.S. or in any particular country or region. In order to market any product outside of the U.S., we or our collaborators 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. Even if we or our collaborators generate the data and information which we believe may be sufficient to file an application for regulatory approval of any of our products or product candidates in a region or country outside the U.S., the relevant regulatory agency may find that we did not meet the requirements for approval, or even if our application is approved, we may have significant post-approval obligations.

Even if we or our collaborators are able to successfully develop our product candidates and obtain marketing approval in a country outside the U.S., we or they 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 or they may obtain may be subject to onerous restrictions such as caps, rebates 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 or that of our collaborators 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 or commencing marketing, if approved, for our product candidates in a country or region outside the U.S. where we or our collaborators have decided it makes business sense to proceed may have a material adverse effect on our business and prospects.

We rely completely on third-party suppliers to manufacture commercial supplies of ZULRESSO and clinical drug supplies for our product candidates, and we intend to rely on third parties to produce commercial supplies of zuranolone, if approved, and non-clinical, clinical and commercial supplies of our approved products and product candidates in the future.

We do not currently have, nor do we plan to acquire or develop, the infrastructure or capability internally to manufacture supplies of ZULRESSO for commercial use, or of zuranolone or 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 rely on our contract manufacturers for commercial supplies of active drug substance, finished drug product and packaged and labeled product with respect to ZULRESSO. We also rely on our contract manufacturers to manufacture sufficient quantities of zuranolone to produce validation batches, and, if zuranolone is approved by the FDA, to manufacture commercial supplies of active drug substance, finished drug product and packaged and labeled product. We also rely on our contract manufacturers to manufacture sufficient quantities of SAGE-324, SAGE-718, SAGE-689 and our other product candidates for ongoing and planned clinical trials and non-clinical studies and expect to rely on them to scale our manufacturing processes for future clinical trials, if our development efforts 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, which we expect to occur in connection with our NDA for zuranolone for the treatment of MDD and PPD, which is under review by the FDA. 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, on the timelines we expect or at all, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities with respect to our products. For example, if the FDA were to find deficiencies in connection with a pre-approval inspection related to our zuranolone NDA submission, the FDA could issue a Form 483 documenting one or more deficiencies, require we provide and comply with a corrective action plan, or determine that our NDA is not approvable in its then-current form.

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 products and product candidates are noncompliant, we may need to find alternative manufacturing facilities, which would significantly adversely delay or impact our commercialization efforts for any approved product and our ability to develop and obtain regulatory approval for our product candidates. Our reliance on contract manufacturers also exposes us to the possibility that they, or third parties with access to their facilities, will have access to and may appropriate our trade secrets or other proprietary information. Also, if a natural disaster were to interrupt or halt production of our drug substance or drug product at one of our third-party contract manufacturers, or cause the loss of batches, we could encounter a supply shortage or face significant costs to rebuild our supply.

We have long-term supply agreements with our contract manufacturers with respect to ZULRESSO drug substance and drug product. 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. We have a long-term supply agreement with our contract manufacturer for zuranolone drug product, but we do not have a long-term supply agreement with any of our contract manufacturing organizations, or CMOs, for zuranolone drug substance and do not have arrangements in place for either long-term supply or redundant supply of drug substance or drug product for SAGE-324 or SAGE-718. Each batch of drug substance and drug product for our product candidates, with the exception of zuranolone drug product, is individually contracted through a purchase order governed by master service and quality agreements.

If our existing CMOs for our other product candidates 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, we could be required to engage new contract manufacturers who would need to scale up the manufacturing process before we would be able to use the drug product or

drug substance they manufacture for clinical trials or for future commercialization, if we are successful and gain approval. In addition, any contract manufacturer will need to 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 would be 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 commercialize any approved product or successfully complete development of our current or future product candidates.

Zuranolone, if approved, or any other future products, if our ongoing development efforts are successful, may not achieve broad market acceptance or reimbursement at sufficient levels, which would limit the revenue that we generate from its sales.

The commercial success of zuranolone, if approved by the FDA, or any of our other current or future product candidates, if successfully developed and approved by the FDA or other applicable regulatory authorities, will depend upon the awareness and acceptance among healthcare professionals, patients, policy-makers and healthcare payors, and reimbursement at sufficient levels.

The availability of coverage and adequacy of reimbursement is essential for most patients to be able to access and afford treatments. Patients who are prescribed medications for the treatment of their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their prescription drugs. Government authorities, including the Centers for Medicare & Medicaid Services, or CMS, an agency within the Department of Health and Human Services, or HHS, in the U.S., 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. Payors may adopt restrictions on coverage for any of our products, including zuranolone, if approved, such as requiring patients to try other lower cost therapies prior to reimbursing our product, requiring patients to meet severity or other criteria more restrictive than the approved label for our product, or requiring onerous and time-consuming prior authorization procedures, or they may limit the amount of reimbursement. These restrictions or limitations might impede appropriate use of our product for the approved indication. Restrictions and limitations on reimbursement or delays in obtaining coverage may vary significantly among payors and payor types. As a result, there is significant uncertainty related to third-party payor coverage and reimbursement of zuranolone, if approved, or any of our other future product candidates, if successfully developed and approved. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is a covered benefit under its health plan; safe, effective and medically necessary; appropriate for the specific patient; cost-effective; and neither experimental nor investigational. Regulatory approvals, pricing and reimbursement for drug products vary widely from country to country.

The inability of us or our collaborators to promptly obtain and maintain coverage and adequate reimbursement rates from both government-funded and private payors for zuranolone, if approved, and any other approved products that we develop could have a material adverse effect on our operating results, our ability to successfully commercialize our products, our ability to raise capital and our overall financial condition. Even if coverage is provided, we may not be able to establish or maintain pricing sufficient to realize a sufficient return on our investment.

Obtaining coverage and reimbursement approval for a product from a government or other third-party payor can be an expensive and time-consuming process that could require us to provide supporting scientific, clinical and cost effectiveness data for the use of our products to the payor. The industry competition to be included in third-party payors' drug formularies, or lists of medications for which third-party payors provide coverage and reimbursement, often leads to downward pricing pressures on pharmaceutical products. In addition, third-party payors may refuse to include a particular branded drug in their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other alternative is available. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors, and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. Increasingly, third-party payors

are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price and best price. Penalties may apply when such metrics are not submitted accurately and on a timely basis. Before granting reimbursement approval, payors may require us to demonstrate that our product candidates, in addition to treating the target indications, also provide incremental health benefits to patients or healthcare costs savings. If zuranolone receives regulatory approval, we plan to pursue a value-based agreement strategy with payors. Payors may not be receptive to the use of value-based agreements or may not agree with our approach and such a strategy may not increase market acceptance or access. If we believe a value-based agreement strategy will not be successful we may change our approach. We cannot be sure that adequate coverage or reimbursement will be available for zuranolone or any other product candidate that we or our collaborators commercialize.

Market acceptance with respect to zuranolone, if approved, or any of our other product candidates that we successfully develop will depend on a number of factors, including, among others:

- the efficacy and safety of our products as demonstrated in clinical trials;
- the potential and perceived advantages and limitations of our products over current or future alternative treatment options, including in the case of zuranolone, if approved, the availability of lower cost antidepressants;
- the incidence and severity of any side effects of the products;
- 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;
- the convenience, benefit, ease and availability of alternative treatments already approved or expected to be commercially launched in the near future;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies, and our ability to increase awareness of our approved products through marketing efforts;
- the strength and effectiveness of our sales, marketing and distribution strategies and support or that of our collaborators;
- publicity concerning our products or competing products and treatments;
- pricing and cost effectiveness; or
- the availability of sufficient third-party coverage or reimbursement, and the willingness of patients to pay out-of-pocket in the absence of such coverage or reimbursement, including in the case of ZULRESSO for both the product and the cost of the infusion.

Our efforts to change the treatment paradigm for a given disorder or to educate the medical community and third-party payors about the benefits of any current or future products, to the extent permitted, including zuranolone for the treatment of MDD and PPD, if approved in those indications, may require significant resources and may never be successful. If zuranolone, if approved, or any other product candidates that may be approved in the future, do not achieve an adequate level of acceptance by patients, physicians, healthcare settings 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 to adequately fund operations or may not do so to the degree or on the timelines we expect.

Even if marketing approval is granted for a product, we may face significant post-marketing obligations and future development and regulatory difficulties.

Regulatory authorities may impose significant and potentially costly post-marketing obligations with respect to approval of any product, including post-marketing studies, additional CMC work and additional pediatric studies. For example, the FDA has imposed post-marketing commitments with respect to approval of ZULRESSO, and we may encounter issues or delays in the conduct of these post-marketing commitments or we may generate unexpected results.

In the event we or our collaborators elect, or are required, to proceed with pediatric studies of any of our product candidates in any indication, regulatory authorities may also require additional non-clinical studies or clinical trials be completed prior to commencement of such pediatric studies.

As was the case with brexanolone, the FDA may recommend controlled substance scheduling for our current or future product candidates, including zuranolone, if approved. In such event, the DEA will need to determine the controlled substance schedule taking into account the recommendation of the FDA. If products are 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. 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. 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. Brexanolone is currently regulated as a Schedule IV controlled substance. Other Schedule IV controlled substances include sedative hypnotics such as benzodiazepines.

ZULRESSO is, and any future approved products 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 required a REMS for ZULRESSO. Any REMS required by the FDA may lead to increased costs to assure compliance with the REMS and 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. In addition, if we are unable to comply with the ZULRESSO REMS or any REMS imposed for a future product, we may face additional restrictions, limitations or substantial penalties, any of which may materially adversely affect our business and results of operations.

We, our collaborators and the third-party manufacturers of our drug substance and drug products and our respective facilities are subject to extensive regulations in the manufacture of our products and product candidates, including GMP, and are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with GMPs and other regulations. If we, our collaborators or a regulatory agency discover problems with our approved products or product candidates such as poor control of production processes or other problems with the facility where our products are manufactured or in the manufacturing process, introduction of contaminants, or adverse events of unanticipated severity or frequency, a regulatory agency may impose restrictions on our products, the manufacturer or us or our collaborators, including requiring withdrawal of such products from the market or suspension of manufacturing. If we, our collaborators, our approved products, our product candidates, or the manufacturers for our products or product candidates fail to comply with applicable regulatory requirements, a regulatory agency may, among other things:

- issue warning letters or untitled letters;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw marketing approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements to applications submitted by us;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products, refuse to permit the import or export of products, or require that we initiate a product recall.

Competing therapies may exist or could emerge that adversely affect the amount of revenue we are able to generate from the sale of ZULRESSO, zuranolone, if approved, or any of our other current or future product candidates, if successfully developed and 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 products or product candidates or address similar markets. It is probable that the number of companies seeking to develop products and therapies similar to our products or targeting similar indications will increase. 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. 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 perceived to be 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.

Currently, there are no pharmacological therapies specifically approved for the treatment of PPD other than ZULRESSO. 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.

Our most advanced product candidate is zuranolone, for which we filed an NDA with the FDA seeking approval for the treatment of MDD and PPD. Patients with MDD are typically treated with a variety of antidepressant medications, including SSRIs, SNRIs and atypical antipsychotics. If approved, zuranolone may also face competition for the treatment of MDD from AXS-05, a combination formulation of an NMDA receptor antagonist, dextromethorphan, with bupropion, an FDA-approved antidepressant affecting norepinephrine and dopamine, which such combination formulation was approved in August 2022 by the FDA for the treatment of MDD in adults. Zuranolone, if approved, may also face competition from esketamine, which is approved for the treatment of treatment-resistant depression and depressive symptoms in adults with MDD with acute suicidal ideation or behavior, and from cariprazine, which was recently approved for the adjunctive treatment of MDD in patients who are receiving ongoing antidepressant therapy. A number of other companies are developing product candidates intended for the treatment of MDD. Furthermore, if zuranolone is successfully approved for PPD and commercialized, it could further limit our commercial opportunity for ZULRESSO.

In the field of neuroactive steroids focused specifically on modulation of $GABA_A$ receptors, we also face competition from a number of companies, including Marinus Pharmaceuticals, Inc., or Marinus. In March 2022, Marinus announced that the FDA had approved ganaxolone, a known $GABA_A$ positive allosteric modulator neuroactive steroid, to treat seizures associated with CDKL5 deficiency disorder, a rare, genetic epilepsy. Other $GABA_A$ competitors include darigabat, which is being developed by Cerevel Therapeutics, Inc. for the treatment of epilepsy and panic disorder.

SAGE-324, a novel $GABA_A$ receptor positive allosteric modulator, is in Phase 2 development for essential tremor. If successfully developed and approved as a treatment for essential tremor, SAGE-324 will face competition from current first-line treatments which include β-adrenergic blocker propranolol and anticonvulsant primidone. Other companies are also developing potential treatments for essential tremor, including a T-type calcium channel modulator that Jazz Pharmaceuticals, Inc. is currently evaluating in Phase 2b development and a Phase 2 T-type calcium channel modulator being developed by Praxis.

A number of companies are working to develop products designed to modulate the NMDA receptor. Aptinyx Inc. has two Phase 2 NMDA receptor modulators in development for multiple indications, targeting two indications each, including NYX-458 being developed for the treatment of cognitive impairment in Parkinson's disease. Novartis AG, following its acquisition of Cadent Therapeutics, Inc., is also developing its own NMDA receptor positive allosteric modulator, CAD-9303, which is currently being investigated in cognitive impairment associated with schizophrenia. In addition, Vaccinex, Inc. is evaluating VX15/2503, a monoclonal antibody against the protein semaphorin 4D (SEMA4D),

as a treatment for cognitive impairment in Huntington's disease. Several companies have developed or are developing products for the treatment of Alzheimer's disease.

Our existing collaborations with Biogen and Shionogi, and any future collaborations, may not lead to the successful development or regulatory approval of product candidates or commercialization of products. Our collaborators may have competing priorities, conflicting incentives, or different views than us on key decisions, including appropriate program spending, that may hamper or delay our development and commercialization efforts or increase our costs. Our business may be adversely affected if any of our collaborators fails to perform its obligations or terminates our collaboration, or if we are not able to establish future collaborations that we believe to be important to our business on commercially reasonable terms.

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 solely ourselves, as well as additional challenges related to operating under a collaboration. For example, we have entered into a collaboration and license agreement with Biogen MA Inc., or BIMA, and Biogen International GmbH, or, collectively with BIMA, Biogen, to jointly develop and commercialize zuranolone and SAGE-324 in the U.S. and granting Biogen rights to develop and commercialize those product candidates in the rest of the world other than Japan, Taiwan and South Korea, or the Shionogi Territory, in the case of zuranolone. We have a separate collaboration with Shionogi & Co., Ltd., or Shionogi, under which we granted rights to Shionogi for the development and commercialization of zuranolone in the Shionogi Territory. The efforts under these collaborations may not be successful and we may never receive any additional milestone payments, profit-share revenue or royalty payments from Biogen or Shionogi. In addition, under most collaborations, including our existing collaborations, a certain degree of control in decision-making is transferred to or shared with our collaborators. Our collaborators may use their decision-making authority to make decisions that could delay, decrease the potential of, or otherwise adversely impact, development and commercialization of our product candidates. Similarly, where we share decision-making authority, the need to gain alignment on decisions may slow or impede advancement of our programs and cause us not to be able to meet our timelines or achieve our goals. Our collaborators may have competing priorities or different incentives that cause them to divert resources away from our collaboration, or we may not agree on appropriate spending levels, which could hamper our overall development and commercialization efforts or increase our overall spending. Our collaborators may independently develop, or develop with a competitor, competitive products or may believe that product candidates being evaluated in the collaboration could be competitive with the collaborator’s own products. In the case of the collaboration with Biogen, both companies have agreed to certain exclusivity provisions for certain products in specified indications which may limit certain development opportunities outside the collaboration. 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 our collaborator fails to perform its obligations under the agreement or the collaboration terminates. 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.

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 additional collaborations on a timely basis, on acceptable terms, or at all.

We may not be successful in our efforts to identify or discover additional product candidates beyond our existing product candidates or to file investigational new drug, or IND, applications for clinical development of new compounds at the rate we expect, 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 upon our and our collaborators' ability to successfully develop, gain approval of and commercialize products based on our current product candidates and on our ability to generate new compounds for development in the future and to successfully complete the non-clinical work necessary to file INDs to pursue clinical development of such new compounds. Our research programs may fail to generate new compounds that meet the standards for non-clinical development, and, if even we are successful in generating such compounds, we may not be able to produce the non-clinical and other data necessary to support IND applications for clinical development, in each case in the number or at the rate we expect or at all for a number of reasons. For example, we may not be able to identify a sufficient number of new targets in areas of interest to us. Our research methodology may be unsuccessful in generating a sufficient number of new compounds appropriate for non-clinical testing in the target areas we identify. Even if we generate new compounds in areas of interest to us, we may determine that those compounds are not appropriate for non-clinical development, or we may generate data in non-clinical development that do not support IND filings for clinical development. We may not have, or devote, sufficient technical, financial, and human resources to our research efforts at the various stages needed to identify targets, generate compounds, conduct non-clinical studies and prepare INDs. Additional 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 not appropriate for further development or unlikely to receive marketing approval. Further, even if we generate new compounds in areas of interest, we may determine that those compounds are not worth pursuing for strategic reasons, including new legislation that may impact the viability of commercializing such compounds, if approved.

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 brain health 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 and may not yield any commercially viable drugs. Our resource allocation decisions may cause us to fail to capitalize on other viable opportunities. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights through future collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain such sole development and commercialization rights. If any of these events occur, it may have a material adverse effect on our business.

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 and shortages, attrition of experienced staff, and other resource constraints;
- fail to comply with contractual obligations;
- fail to comply with current Good Clinical Practices, or GCPs, or experience other regulatory compliance issues;

- undergo changes in priorities or become financially distressed;
- form relationships with other entities, some of which may be our competitors; or
- be impacted by the downstream effects of the COVID-19 pandemic, including changes to the macroeconomic environment in ways that adversely affect our business.

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 and regulatory requirements, and scientific standards, and our reliance on CROs does not relieve us of our regulatory responsibilities. We, clinical investigators, and our CROs are required to comply with regulations and guidelines, including GCPs, 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, or EEA, and comparable foreign regulatory authorities for any product candidates in clinical development or where clinical trials are being conducted. If we or our CROs or contract manufacturers fail to comply with these regulations or if the quality or accuracy of the clinical data obtained is compromised due to the failure to adhere to our clinical protocols or other regulatory requirements or for other reasons, and we are unable to rely on clinical data collected, we may be required to repeat clinical trials or extend the duration of, or increase the size of our clinical trials. This 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 or if a CRO needs to be replaced, we may not be able to enter into arrangements with alternative CROs in a timely manner or at all. Any of these issues could significantly delay or prevent regulatory approval of our product candidates and require significantly greater expenditures. In such an event, we believe that our financial results might be harmed, our costs could increase and our ability to generate revenue from products beyond ZULRESSO could be delayed.

As our development and commercialization efforts advance, we expect to continue to significantly develop and expand our company, and we may encounter difficulties in managing this development and expansion, which could disrupt our operations.

Given the complexity and level of activities and resources that are necessary to develop and commercialize pharmaceutical products, we have been growing and expanding our company and, if our planned development and regulatory efforts are successful, we expect to continue to need to significantly increase our number of employees and the scope of our operations. For example, to commercialize any future products, we will need to recruit and train additional qualified sales personnel, and continue to implement and improve our managerial, operational and financial systems. We may not be able to effectively manage any expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure and give rise to operational mistakes or delays, loss of business opportunities, loss of employees and reduced productivity among remaining employees. If our management is unable to effectively manage any potential significant 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 any future products that we successfully develop, and to compete effectively will depend, in part, on our ability to effectively manage the potential future expansion of our company.

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

To accomplish our objectives, we require a strong management team with expertise in research and development, clinical development and commercialization. Although we have entered into employment agreements with each of our executive officers, each of them is employed "at will" and may terminate his or her employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees. Recruiting and retaining qualified personnel is 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 personnel. If we are

unable to continue to attract and retain high quality personnel, our development efforts, commercialization activities, business, financial condition, results of operations and growth prospects could be adversely affected.

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

The sale of ZULRESSO and any future approved products and use of our product candidates in clinical trials will expose us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers or others using, prescribing, selling or otherwise coming into contact with our products and product candidates. For example, we may be sued if any product or product candidate 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 laws. If we become subject to product liability claims and cannot successfully defend ourselves against them, we could incur substantial liabilities. 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 approved products;
- 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
- withdrawal of products from the market or our inability to successfully gain approval of product candidates.

We maintain product liability insurance coverage with a $20.0 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. 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.

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, which we participate in, and other governmental programs impose obligations to report pricing figures to the federal government, require us to pay rebates and participate in discount programs. Other programs impose limits on the price we are permitted to charge certain entities for ZULRESSO or for any future 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 ZULRESSO or any future products for which we receive regulatory approval and could negatively impact our results of operations. Our failure to comply with these price reporting and rebate payment obligations could negatively impact our financial results. The Patient Protection and Affordable Care Act, as amended, referred to herein as the ACA, and regulations promulgated thereunder could affect our obligations in ways we cannot anticipate.

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. If we become obligated to restate or recalculate the amounts we report under these programs, our costs for complying with the laws and regulations governing the Medicaid Drug Rebate Program and our price discounts and rebates could be increased. Additionally, we could be held liable for errors associated with our submission of pricing data under the Medicaid Drug Rebate Program and other federal or state drug pricing programs, including retroactive rebates and program refunds, and if we are found to have knowingly submitted false average manufacturer price or best price information to the government, civil monetary penalties per item of false information. Certain failures to submit required data could result in a civil monetary penalty for each day the information is late beyond the due date and be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we participate in the Medicaid program, or, if we fail to comply with 340B program requirements, the Health Resources and Services Administration, or HRSA, could decide to terminate our 340B program participation agreement. In the event that CMS terminates our rebate agreement or HRSA terminates our 340B program participation agreement, no federal payments would be available under Medicaid or Medicare Part B for our covered outpatient drugs. We are also subject to civil monetary and other penalties applicable to the drug pricing negotiation program and Part B and Part D inflation rebate programs, as discussed further below under the risk factor entitled "*Healthcare regulations aimed at reducing healthcare costs may have a material adverse effect on our business or results of operation*."

We are subject to other laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

We are subject to a number of healthcare and other statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we currently or may in the future conduct our business.

Our current or future interactions and arrangements with third-party payors, healthcare providers, patients, healthcare settings, and others who play a role in the recommendation, prescription, reimbursement and administration of ZULRESSO and will play a similar role with respect to zuranolone, if approved and any of our other future product candidates, if successfully developed and approved, are governed in part by broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute ZULRESSO or expect to market, sell and distribute any future approved products. 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 (including any kickback, bribe or certain rebates), 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. This statute has been interpreted to apply to arrangements between pharmaceutical companies on the one hand, and prescribers, purchasers and formulary managers, among others, on the other.
- 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, with potential liability including mandatory treble damages and significant per-claim penalties. Pharmaceutical companies have been prosecuted under the False Claims Act in connection with their alleged off-label promotion of drugs, purportedly concealing price concessions in the pricing information submitted to the government for government price reporting purposes, and allegedly providing free product to customers with the expectation that the customers would bill federal health care programs for the product, among other activities. 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 False Claims Act.

- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes privacy, security and breach reporting obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information upon covered entities subject to the rule.
- 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 ACA 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 HHS information related to physician payments and other transfers of value made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Effective January 1, 2022, these reporting obligations were extended to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners.
- 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.
- Various federal and state health information and data protection laws and regulations, and similar types of laws outside the U.S., govern the collection, use, disclosure and protection of health-related and other personal information by us and our collaborators.

Ensuring that our future practices and business arrangements comply with applicable healthcare laws and regulations is 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 activities conducted by our commercial team or other of our employees, consultants or vendors, 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. We may also be substantially negatively impacted if governmental authorities conclude that the business practices of one of our collaborators does not comply with applicable laws. 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.

We and our employees are also subject to other statutes and regulations related to our business, including: regulations imposed by the FDA and applicable non-U.S. regulators, as previously discussed; anti-bribery and anti-corruption laws and regulations applicable to activities outside the U.S.; rules on reporting financial and other information or data timely and accurately; and rules related to insider trading.

Although we have adopted a code of conduct and have an active compliance program, 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 by our employees to comply with these laws or regulations.

Data collection is governed by restrictive regulations governing the use, processing, and cross-border transfer of personal information.

We must comply with numerous federal, state and non-U.S. laws which govern the privacy and security of health and other personal information. As described above, to the extent applicable to our business activities, HIPAA imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information. In addition, when we conduct clinical trials in the U.S., any personal information that is collected in connection with these trials also is regulated by the Federal Policy for the Protection of Human Subjects (the Common Rule) which creates obligations for our company when conducting these trials.

We plan to enroll subjects in our ongoing or future clinical trials in the European Union, or EU, or other countries. When we do so, we may be subject to additional privacy restrictions, including restrictions relating to the collection, use, storage, transfer, and other processing of personal data, including personal health data, regarding these individuals. Clinical trial activities in the EEA, for example, are governed by the General Data Protection Regulation, or GDPR, in relation to the processing of personal data. The GDPR imposes several requirements on companies that process personal data, strict rules on the transfer of personal data out of the EEA, including to the U.S., and fines and penalties for failure to comply with the requirements of the GDPR and the related national data protection laws of the EU Member States. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR in some situations. The obligations under the GDPR may be onerous and adversely affect our business, financial condition, results of operations and prospects. Compliance with the GDPR is a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any European activities. The issues related to the transfer of personal data are subject to substantial uncertainty at this time, and there can be no reasonable level of confidence that any such data transfers will be found to be consistent with EU law if they are challenged. The United Kingdom's, or UK's, exit from the EU, often referred to as Brexit, has created uncertainty with regard to future data protection regulation in the United Kingdom. The European Commission has adopted an adequacy decision concerning the level of data protection in the UK. Personal data may now flow freely from the EEA to the UK; however, the European Commission may suspend the adequacy decision if it decides that the UK no longer provides for an adequate level of data protection. Similar laws exist in many other countries around the world, and these laws (which are evolving and expanding) create complicated and potentially inconsistent obligations that may impact our business.

We are also subject to the California Consumer Privacy Act, or CCPA, which creates individual privacy rights for California consumers (as defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. While there is currently an exception for protected health information that is subject to HIPAA and clinical trial regulations, as currently written, the CCPA may impact our business activities. The CCPA also has been amended through a recent referendum in California that creates additional obligations that went into effect on January 1, 2023. In November 2020, California voters approved the California Privacy Rights Act, or CPRA, ballot initiative which introduced significant amendments to the CCPA and established and funded a dedicated California privacy regulator, the California Privacy Protection Agency, or the CPPA. New implementing regulations will be issued under the CPRA that may lead to new or additional obligations for us. Failure to comply with the CCPA may result in, among other things, significant civil penalties and injunctive relief, or statutory or actual damages. In addition, California residents have the right to bring a private right of action in connection with certain types of incidents. These claims may result in significant liability and damages. At least four states have passed similar general privacy legislation that may impact our business activities in the future, and additional states are evaluating similar kinds of general privacy legislation. In addition, there are substantial efforts at the federal level to pass a national data privacy law that may impact our business activities. The uncertainty, ambiguity, complexity and potential inconsistency surrounding the implementation and interpretation of CCPA and other enacted or potential laws in other states and at the federal level exemplify the vulnerability of our business to the evolving regulatory environment related to the privacy, security and confidentiality of personal data and protected health information. We may be subject to fines, penalties, or private actions in the event of non-compliance with such laws. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products. We have implemented processes to manage compliance with the CCPA and continue to assess the impact of the CPRA, and other federal and state legislation, on our business as additional information and guidance becomes available.

In addition to the foregoing, any breach of privacy laws or data security laws, particularly resulting in a significant security incident or breach involving the misappropriation, loss or other unauthorized use or disclosure of sensitive or confidential patient or consumer information, could have a material adverse effect on our business, reputation and

financial condition. As a data controller, we will be accountable for any third-party service providers we engage to process personal data on our behalf, including our CROs. There is no assurance that privacy and security-related safeguards we implement will protect us from all risks associated with the third-party processing, storage and transmission of such information. In certain situations, both in the U.S. and in other countries, we also may be obligated as a result of a security breach to notify individuals and/or government entities about these breaches.

Additionally, in October 2022, President Joe Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-U.S. Privacy Shield. The European Commission initiated the process to adopt an adequacy decision for the EU-U.S. Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may impact our activities with companies in the EU, and any potential future business operations in the EU.

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, and enforce laws and regulations prohibiting the promotion of unapproved, or "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 taken steps to restrict promotional activities of those companies. Pharmaceutical companies have also been prosecuted and incurred significant civil, criminal and administrative penalties, damages, fines under the False Claims Act in connection with their alleged off-label promotion of drugs. Any promotion of the off-label use of ZULRESSO, zuranolone, if approved, or any of our other future approved products by us or any of our employees could subject us to significant liability, which would materially adversely affect our business and financial condition.

Our future growth may depend, in part, on our ability to penetrate foreign markets, where we would be subject to additional regulatory burdens, price controls, reimbursement issues and other risks and uncertainties, and could negatively impact our U.S. business.

Our future profitability may depend, in part, on our ability, ourselves or through our collaborators, to commercialize our products and product candidates in foreign markets.

The pricing of prescription pharmaceuticals in foreign markets is subject to foreign governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of regulatory approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired.

In some countries, including Member States of the EU, the pricing of prescription drugs is subject to governmental control. Additional countries may adopt similar approaches to the pricing of prescription drugs. There can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after coverage and reimbursement have been obtained. Reference pricing used by various countries and parallel distribution, or arbitrage between low-priced and high-priced countries, can further reduce prices. In the U.S., recent legislative and administrative policies and proposals signal a desire to lower drug prices in the U.S. As a result, we or our collaborators outside the U.S. in the future may be limited in the prices we are able to charge for our products in the U.S. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If pricing is set at unsatisfactory levels or if reimbursement of our products is unavailable or limited in scope or amount, our revenues from sales by us or our collaborators and the potential profitability of our products in those countries would be negatively affected.

Commercializing our products and product candidates in foreign markets would subject us to additional risks and uncertainties, including:

- 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, including the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer accounts receivable collection times;
- reduced protection of intellectual property rights, and the existence of additional potentially relevant third-party intellectual property rights, in some foreign countries; and
- foreign currency exchange rate fluctuations.

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. For example, Brexit has already and may continue to adversely affect European and/or worldwide regulatory conditions. Brexit could continue to lead to legal uncertainty and potentially divergent national laws and regulations in the EU and the United Kingdom, including those related to the pricing of prescription pharmaceuticals, as the United Kingdom determines which EU laws to replicate or replace, which could impair our ability to transact business in the EU and the United Kingdom in the future, if we elect to seek to commercialize any of our products there.

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.

We cannot provide any assurances that any of our pending patent applications will mature into issued patents. For example, the U.S. Patent and Trademark Office, or U.S. PTO, has issued a final rejection against one of our patent applications claiming one of our proprietary $GABA_A$ positive allosteric modulator compounds, asserting a lack of novelty and non-obviousness. We are in the process of challenging the rejection, and may not be successful in overturning the rejection.

We may be unable to obtain issued patents covering our proprietary compounds. We cannot provide any assurances that any of our issued 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 issued patent and patent applications that 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, such issued patent and any patent that may issue from such patent applications, would not prevent third-party competitors from creating, making and marketing alternative formulations of brexanolone that fall outside the scope of the patent claims or from practicing alternative methods. 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, derivation proceedings, *ex parte* reexamination, or *inter partes* review proceedings, post-grant 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. For example, our granted European patent covering brexanolone i.v. has been opposed by a third party, and the opposition proceedings are ongoing. 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 or a derivation 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 also 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 or product candidates is 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 generate significant revenue from sales of ZULRESSO or any of our product candidates, if successfully developed and 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 provide us with a competitive advantage and be found ultimately to 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 ZULRESSO, zuranolone, if approved, and our other product candidates, if successfully developed and 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 products or 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 our current product candidates and commercialize ZULRESSO and any 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 or 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 or 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.

Most of our employees have also 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. 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 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. 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 should be interpreted narrowly and 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 or derivation 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 or any of our product candidates could be found invalid or unenforceable if challenged in court.

If we or one of our collaborators or licensors initiated legal proceedings against a third party to enforce a patent, if and when issued, covering our product or any of our product candidates, the defendant could counterclaim that the patent covering our product or any of our product candidates 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, lack of written description, 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, *inter partes* review, derivation proceedings or interferences and equivalent proceedings in foreign jurisdictions, e.g., opposition or revocation 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. For example, our granted European patent covering brexanolone i.v. has been opposed by a third party, and the opposition proceedings are ongoing. 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 the applicable product or 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. Further, they 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 2022 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 in such jurisdictions. 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, among other things, 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 ZULRESSO and 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 products or product candidates, if approved. If we breach any of the agreements under which we license the use, development and commercialization rights to our products, 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. If we fail to obtain a license, 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 licenses or 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 commercialize the relevant product or to successfully develop and commercialize the affected product candidates.

We have entered into several licenses to support our various programs. We may enter into additional 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 a product candidate or commercialize a product, 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 of the University of California 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 product or 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 product 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 our product candidates and if we do not obtain additional protection under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as 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 sell or 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 have obtained NCE exclusivity for brexanolone and plan to seek NCE exclusivity for our current and future product candidates. There is no guarantee that our product candidates will qualify for marketing or data exclusivity under these provisions or that such exclusivity for any of our products will alone be sufficient for our business. The applicable five-year and three-year exclusivity periods of NCE or data exclusivity under the FDCA 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 U.S. patents we own or license may be eligible for limited patent term restoration in the future under 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 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 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.

Our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involves both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the U.S. has recently enacted 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 are 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, 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. For example, in March 2012, in *Mayo Collaborative Services, DBA Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc.*, the U.S. Supreme 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, in June 2013, in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the U.S. Supreme 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. In June 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 U.S. Supreme 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 has 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. The full impact of these decisions on our business is not yet known.

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.

With passage of the CREATES Act, we are exposed to possible litigation and damages by competitors. In addition, existing statutes, including the CREATES Act, and proposed legislation in Congress, if passed into law, could limit the patent exclusivity on our products or facilitate earlier entry of generic competition.

Under the CREATES Act, legislation intended to facilitate the development of generic and biosimilar products, we are exposed to possible litigation and damages by competitors who may claim that we are not providing sufficient quantities of our approved products on commercially reasonable, market-based terms for testing in support of their ANDAs and 505(b)(2) applications. Such litigation would subject us to additional litigation costs, damages and reputational harm, which could lead to lower revenues. Increased risk of generic competition with ZULRESSO, zuranolone, if approved, and any of our other product candidates, if approved, including as a result of the CREATES Act, could impact our ability to maximize product revenue.

In addition, members of Congress have proposed numerous legislative initiatives aimed at limiting the patent exclusivity on drug products or facilitating earlier entry of generic versions of approved drugs. Examples of bills that have been proposed include a bill that, if passed, would create a presumption of invalidity for patents beyond the first patent covering a drug product thus shifting the burden to the innovator to prove that these subsequent patents are separately patentable inventions, distinct from the first patent; a bill that, if passed, would empower the Federal Trade Commission to investigate whether large patent portfolios covering a drug product constitute an anti-competitive practice and to file antitrust lawsuits in such instances; and a bill that, if passed, would limit the availability of a 30-month stay on approval by the FDA of a generic version of a drug to only those instances where the ANDA litigation involves a composition of

matter patent claiming the drug substance. Such legislation, if passed into law, could adversely affect ZULRESSO or any future products or result in earlier entry into the market of generic versions of our drugs.

Risks Related to our Industry

Healthcare regulations aimed at reducing healthcare costs may have a material adverse effect on our business or results of operations.

There have been, and likely will continue to be, legislation and legislative, administrative and regulatory proposals in the U.S., both at the federal and state level, and in many foreign jurisdictions, aimed at reducing healthcare costs. The implementation of cost containment measures, drug pricing controls or other reforms could have an adverse effect on our revenue from ZULRESSO, zuranolone, if approved, or from the sales of any other products that are successfully developed and approved, and may limit our ability to achieve profitability.

For example, in March 2010, the ACA was passed, which substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacted the U.S. pharmaceutical industry. The ACA, among other things, subjects biological products to potential competition by lower-cost biosimilars, provided a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% (pursuant to the Bipartisan Budget Act of 2018, effective as of 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D (subsequently modified by the IRA, as discussed below).

Certain provisions of the ACA have been subject to judicial challenges as well as efforts to modify them or to alter their interpretation or implementation. For example, the U.S. Tax Cuts and Jobs Act of 2017, signed into law in December 2017, included 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." We expect that the ACA, its implementation, efforts to challenge or modify the ACA or its implementing regulations, or portions thereof, 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.

There has been increasing legislative and enforcement interest in the U.S. with respect to drug pricing practices. Specifically, there have been several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs, including under Medicare and Medicaid, which may potentially impact negotiations on pricing and discounts with commercial payers, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. There have been multiple Congressional and administrative efforts to address drug pricing, including the Inflation Reduction Act of 2022, or IRA. It is unclear whether any other legislation or public policy will come to pass, and if so, what effect it could have on our business.

The IRA was signed into law by President Biden in August 2022. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for certain outpatient prescription drug coverage, as well as Medicare Part B. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare, with negotiated prices subject to a cap and first set to take effect in 2026; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (the first Part B inflation rebate period is in first quarter 2023; the first Part D inflation rebate period is fourth quarter 2022 through third quarter 2023); and replaces the Part D coverage gap discount program with a new Part D discounting program (beginning in 2025). The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years of these programs. Manufacturers may be subject to civil monetary penalties for certain violations of the negotiation and inflation rebate provisions and an excise tax during a noncompliance period under the negotiation program.

Specifically, with respect to price negotiations, Congress authorized CMS to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. Drugs may be selected for negotiation only once they are at least seven years post-approval (such that they will be nine years post approval when first subject to the maximum negotiated price) and biologics may be selected for negotiation 11 years post approval (such that they will be 13 years post-approval when first subject to the maximum negotiated price). It does not apply to drugs and biologics that have been approved for a single rare disease or condition. We could be at risk of government action if, in the future, any of our products are the subject of Medicare price negotiations. In that event, the outcome of the Medicare price negotiations, which will be made publicly available, may also impact negotiations on pricing and discounts with commercial payers. These risks as to pricing may further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if the pricing of any of our products are the subject of Medicare price negotiations. As a result, these risks may also impact the development decisions we make with respect to our products.

Further, the IRA subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the IRA by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The IRA also requires manufacturers to pay rebates for drugs reimbursed under Medicare Part D whose price increases exceed inflation and caps Medicare out-of-pocket drug costs beginning in 2025, at $2,000 a year, subject to an adjustment for inflation thereafter. Drug manufacturers may also be subject to civil monetary penalties with respect to their compliance with these programs. In addition, the IRA potentially raises risks related to individuals participating in a Medicare Part D prescription drug plan who may experience a gap in coverage if they required coverage above their initial annual coverage limit before they reached the higher threshold, or "catastrophic period" of the plan. Individuals requiring services exceeding the initial annual coverage limit and below the catastrophic period, must pay 100% of the cost of their prescriptions until they reach the catastrophic period. Among other things, the IRA contains many provisions aimed at reducing this financial burden on individuals by eliminating the coverage gap starting in 2025, reducing the co-insurance and co-payment costs, expanding eligibility for lower income subsidy plans, and imposing price caps on annual out-of-pocket expenses, each of which could have potential pricing and reporting implications.

It is unclear how the IRA will be implemented. We further cannot predict with certainty what impact the IRA or any other federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition. There may be additional Congressional and administrative efforts to address drug pricing.

At the state level, legislatures have increasingly passed legislation and agencies have implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and price transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at containing or lowering the cost of healthcare or limiting exclusivity periods for pharmaceutical products. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for ZULRESSO and for zuranolone, if approved, or any of our other product candidates, if approved;
- our ability to receive or set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the amount of taxes that we are required to pay; and
- the availability of capital.

We expect that the measures discussed above, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, lower reimbursement, and new payment methodologies. This could lower the price that we receive for any approved product. Any denial in coverage or reduction in reimbursement from Medicare or other government-funded programs may result in a similar denial or reduction in payments from private payors, which may prevent us from being able to generate sufficient revenue from sales of ZULRESSO, successfully commercialize zuranolone or any other products if approved in the future, and achieve profitability.

Our internal computer systems or networks, or cloud platforms or those of our collaborators, our third-party CROs or our other contractors, consultants or service providers, may fail or suffer security breaches, which could result in a material disruption of our development programs, compromise personal or sensitive information related to our business, or cause us to incur significant liabilities which could adversely impact our business.

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business, and despite the implementation of security measures, our internal computer systems and those of our collaborators, our third-party CROs and our other contractors, consultants and service providers are vulnerable to cyber security threats, including damage from unauthorized access, theft, natural disasters, terrorism, war, telecommunication and electrical failures, and system malfunction, or from cyber-attacks by malicious third parties (including the deployment of harmful malware, ransomware, viruses, worms, denial-of-service attacks, supply chain attacks, social engineering schemes and other means to affect service reliability and threaten the confidentiality, integrity and availability of information). 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, disaster 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 could be required to expend significant amounts of money and other resources to respond to these threats or breaches and to repair or replace information systems or networks or cloud platforms. We also could suffer financial loss or the loss of valuable confidential information. In addition, we could be subject to regulatory actions and/or claims made by individuals and groups in private litigation involving privacy issues related to data collection and use practices and other data privacy laws and regulations, including claims for misuse or inappropriate disclosure of data, as well as unfair or deceptive acts or practices in violation of Section 5(a) of the Federal Trade Commission Act, or the FTC Act. The Federal Trade Commission, or the FTC, expects a company's data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities. Individually identifiable health information is considered sensitive data that merits stronger safeguards. The guidance of the FTC for appropriately securing consumers' personal information is similar to what is required by the HIPAA Security Rule, which establishes national standards for covered entities to protect individuals' electronic personal health information. The HIPAA Security Rule requires covered entities to have appropriate administrative, physical and technical safeguards to help ensure the confidentiality, integrity, and security of electronic protected health information. With respect to privacy, the FTC also sets expectations that companies honor the privacy promises made to individuals about how the company handles consumers' personal information. Any failure to honor promises, such as the statements made in a privacy policy or on a website, may also constitute unfair or deceptive acts or practices in violation of the FTC Act. While we do not intend to engage in unfair or deceptive acts or practices, the FTC has the power to enforce promises as it interprets them, and events that we cannot fully control, such as data breaches, may be result in FTC enforcement. Enforcement by the FTC under the FTC Act can result in civil penalties or enforcement actions.

Although we develop and maintain systems and controls designed to prevent these events from occurring and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes are costly and require ongoing monitoring and updating as technologies change and efforts to overcome security measures become increasingly sophisticated. Moreover, we cannot guarantee that our, or our third-party CROs' or our other contractors', consultants' or service providers' security measures will be sufficient to prevent data loss and other security

breaches. Despite our efforts, the possibility of these events occurring cannot be eliminated entirely and there can be no assurance that any measures we take will prevent cyber-attacks or security breaches that could adversely affect our business, including security breaches that may remain undetected for extended periods of time, which can substantially increase the potential for a material adverse impact resulting from the breach.

Risks Related to Our Financial Position and Need for Capital

We are a biopharmaceutical company that has not generated significant revenue to date. We have incurred significant operating losses since our inception, and anticipate that we will incur losses for the foreseeable future.

We are a biopharmaceutical company with only one approved product, and only began generating revenue from product sales in the second quarter of 2019.Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk.

We have funded our operations to date primarily through proceeds from sales of common stock, including the sale of stock to BIMA; redeemable convertible preferred stock prior to our initial public offering and, to a lesser extent, the issuance of convertible notes. From our inception through December 31, 2022, we had received aggregate net proceeds of $2.8 billion from such transactions. We also received $1.0 billion in upfront payments under our collaborations with Biogen and Shionogi. As of December 31, 2022, our cash, cash equivalents and marketable securities were $1.3 billion. We have incurred net losses in each year since our inception, except for net income of $606.1 million for the year ended December 31, 2020, reflecting revenue recognized under a collaboration and license agreement with Biogen. Our net loss was $532.8 million for the year ended December 31, 2022, and our accumulated deficit was $2.0 billion as of December 31, 2022.

Substantially all of our operating losses have resulted from costs incurred in connection with our research and development programs and from selling, 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' equity and working capital. We expect our research and development expenses and selling, general and administrative expenses to increase, particularly as we advance planned and ongoing clinical trials for SAGE-718 and SAGE-324 and prepare for the potential commercial launch of zuranolone, including in support of permitted pre-launch and launch-readiness activities associated with zuranolone. In addition, if we obtain marketing approval for zuranolone or any of our other current or future product candidates beyond ZULRESSO, we would expect to incur significant sales, marketing and outsourced-manufacturing expenses. We incur significant legal and accounting costs associated with operating as a public company. We expect to continue to incur additional 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 and/or revenue from our collaborations on a sustained basis. We began to generate revenue from product sales in the second quarter of 2019 in conjunction with launch of our first product, ZULRESSO, which commenced in June 2019. We expect that our revenue opportunity for ZULRESSO will continue to be limited. Our ability to generate significant product revenue from any future approved product depends on a number of factors, including, but not limited to:

- our ability to successfully obtain marketing approval of zuranolone in the U.S. for the indications and on the timelines we expect;
- 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 other product candidates; and our ability to file for and receive marketing approval to commercialize our product candidates, if successfully developed; and
- with respect to zuranolone, if approved, and any other approved product, our ability, alone or with collaborators, to commercialize the product by developing and effectively deploying a sales force, and to achieve market

acceptance and satisfactory reimbursement of such product in the medical community, with patients and with third-party payors.

If we are unable to generate significant product revenue and/or revenue from our collaborations on a sustained basis, we will not become profitable, and may be unable to continue operations without continued funding.

We may need to raise additional funding at some point in the future, 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. 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 other strategic considerations. 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.

We are currently commercializing ZULRESSO, have filed for marketing approval of zuranolone in the U.S. for the treatment of adults with MDD and PPD, have begun our permitted pre-launch and launch-readiness activities associated with the potential approval of zuranolone, and are advancing our other product candidates through non-clinical and clinical development. Commercializing a product and developing additional small molecule products are expensive. We expect our research and development expenses and selling, general and administrative expenses to increase, particularly as we advance planned and ongoing clinical trials for SAGE-718 and SAGE-324 and prepare for the potential commercial launch of zuranolone, including in support of permitted pre-launch and launch-readiness activities associated with zuranolone. We expect we will require additional capital in the future to fund operating needs. We may need to raise additional funds sooner if we choose to pursue additional indications and/or geographies for our product candidates, conduct additional clinical trials for indications we are already pursuing beyond the anticipated trials, identify new potential opportunities or otherwise expand our activities more rapidly than we presently anticipate.

As of December 31, 2022, our cash, cash equivalents and marketable securities were $1.3 billion. We expect that our existing cash, cash equivalents and marketable securities, in addition to anticipated funding from our ongoing collaborations, excluding revenues and milestones, will be sufficient to fund our anticipated level of operations through 2024. 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, licensing arrangements and arrangements involving other rights or a combination of these or other approaches. In any event, we anticipate we will require additional capital to expand future development efforts for, obtain regulatory approval for, and to commercialize our product candidates. If current or future economic conditions impact capital markets for an extended period, or if our business prospects are impaired or the capital markets disrupted for any other reason, additional capital may not be available to us on acceptable terms, or at all. Failure to obtain capital if and when needed may force us to delay, limit or terminate our product development efforts or other operations. 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 other strategic considerations.

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, our stock price is likely to decline which would make a future financing more difficult and potentially more dilutive to our existing stockholders. For example, after the announcement of the topline results of the Phase 3 MOUNTAIN Study of zuranolone on December 5, 2019, our stock price declined significantly. In addition, future global economic uncertainty, reduced liquidity, capital market disruptions, and other macroeconomic or geopolitical conditions may potentially make it more difficult for us to raise additional funds on favorable terms. 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 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.

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. 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.

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 approved product, 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.

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 success or failure of our efforts to: receive FDA approval of our NDA for zuranolone for the treatment of MDD and PPD on a timely basis or at all;
- the results of our commercialization efforts with respect to zuranolone, if approved, and our ability to attain commercial success;
- plans for, progress of, timing of, changes to, delays in or results from clinical trials or non-clinical studies of any of our 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;
- the success or failure of any regulatory activities with respect to our other existing or future product candidates beyond zuranolone;
- announcements of new products, technologies, commercial relationships, acquisitions, collaborations or other events by us or our competitors;
- the success or failure of our 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 future product candidates, if successfully developed and approved, to achieve commercial success;
- fluctuations in stock market prices and trading volumes of similar companies;
- the state of the U.S. and world economies, general market conditions and overall fluctuations in U.S. equity markets, including as a result of U.S. or world events;
- 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;
- the impact of the COVID-19 pandemic and its downstream effects, as well as other macroeconomic trends and geopolitical events;
- 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.

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

We have considerable discretion in the use of our cash and the application of the net proceeds from potential future follow-on public offerings. We may use cash and 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 any potential future 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.

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. For example, the 6,241,473 shares of our common stock purchased by BIMA were subject to an 18-month lockup period, which expired on June 30, 2022, after which BIMA is able to sell a certain amount of its shares, subject to certain sales and volume limitations, or, if BIMA requests registration of its shares pursuant to its registration rights, without such sales and volume limitations. Following a second 18-month period, which expires December 31, 2023, BIMA will be able to sell shares without limitation.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters are located in Cambridge, Massachusetts. We lease 63,017 square feet of office space in a multi-tenant building pursuant to a lease dated as of December 2011, as amended in March 2019, that will expire on August 31, 2024.

In May 2016, we entered into a lease, as amended in April 2018, under which we rent 40,419 square feet of additional office space in a separate multi-tenant building in Cambridge, Massachusetts. The term for this lease will expire on August 31, 2024.

We have entered into other non-material leases and may lease additional space prior to the expiration of our leases to meet the needs of the business.

Item 3. Legal Proceedings

We may from time to time become involved in legal proceedings relating to claims arising from our ordinary course of business, including claims related to contracts, employment arrangements, operating activities, intellectual property or other matters. We are not currently subject to any legal proceeding that we believe would have a material adverse impact on our financial position, results of operations or cash flows or other material legal proceeding.

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 8, 2023, there were six 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 January 1, 2018 through December 31, 2022, to two indices: the Nasdaq Composite Index and the Nasdaq Biotechnology Index. The graph assumes an initial investment of $100 on December 31, 2017 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 December 31, 2017 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 Annual Report 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.

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. [Reserved]

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, for the year ended December 31, 2022, or Annual Report. In addition to historical information, this discussion and analysis contains forward-looking statements that involve risks, uncertainties and assumptions. We caution you that forward-looking statements are not guarantees of future performance, and that our actual results of operations, financial condition and liquidity, and the developments in our business and the industry in which we operate, may differ materially from the results discussed or projected in the forward-looking statements contained in this Annual Report. We discuss risks and other factors that we believe could cause or contribute to these potential differences elsewhere in this Annual Report, including under Part I, Item 1A, "Risk Factors" and under "Cautionary Note Regarding Forward-Looking Statements" in this Annual Report. In addition, even if our results of operations, financial condition and liquidity, and the developments in our business and the industry in which we operate are consistent with the forward-looking statements contained in this Annual Report, they may not be predictive of results or developments in future periods. We caution readers not to place undue reliance on any forward-looking statements made by us, as such statements 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.

Information pertaining to fiscal year 2020 was included in the Company's Annual Report on Form 10-K for the year-ended December 31, 2021, on pages 89 through 110, under Part II, Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations," which was filed with the SEC on February 24, 2022.

Overview

We are a biopharmaceutical company with a mission to pioneer solutions to deliver life-changing brain health medicines, so every person can thrive. We are currently targeting diseases and disorders of the brain with three key focus areas: depression, neurology and neuropsychiatry. Our focus as a company is on brain health, and we are currently targeting two critical central nervous system, or 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.

Our first product, ZULRESSO® (brexanolone) CIV injection, is approved in the U.S. for the treatment of postpartum depression, or PPD, in adults. We launched ZULRESSO commercially in the U.S. for the treatment of PPD in June 2019. ZULRESSO may only be administered in qualified, medically-supervised healthcare settings. Brexanolone is chemically identical to allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors.

We also are developing a portfolio of other novel compounds that target $GABA_A$ receptors including our most advanced product candidate, zuranolone (SAGE-217). Zuranolone is a novel oral compound for the treatment of major depressive disorder, or MDD, and PPD. In December 2022, we, and our collaboration partner, Biogen, completed submission of a new drug application, or NDA, to the U.S. Food and Drug Administration, or FDA, seeking approval of zuranolone for the treatment of both MDD and PPD. The NDA was accepted for filing and granted priority review by the FDA in February 2023, with a Prescription Drug User Fee Act, as amended, or PDUFA, target action date of August 5, 2023. The FDA granted Fast Track designation to zuranolone for the treatment of PPD in early 2022 and previously granted zuranolone Breakthrough Therapy designation and Fast Track designation to zuranolone for the treatment of MDD. Zuranolone is a neuroactive steroid that, like brexanolone, is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extrasynaptic $GABA_A$ receptors.We may in the future develop zuranolone for other affective disorders.

To date, we have completed six pivotal clinical trials of zuranolone, four in MDD and two in PPD. The completed pivotal trials evaluating zuranolone for the treatment of PPD and three of the four completed pivotal trials evaluating

zuranolone for the treatment of MDD met their primary endpoints. We announced results from the following clinical trials of zuranolone in either 2021 or 2022:

- **SKYLARK Study (completed)**

  In June 2022, we announced that the SKYLARK Study, a Phase 3 placebo-controlled clinical trial evaluating a two-week course of zuranolone 50 mg in women with PPD, met its primary and all key secondary endpoints.

- **CORAL Study (completed)**

  In February 2022, we announced that the CORAL Study, a placebo-controlled Phase 3 clinical trial evaluating a two-week course of zuranolone 50 mg, when co-initiated with a newly administered open-label standard antidepressant therapy, or ADT, compared with open-label standard of care ADT co-initiated with placebo, as an acute rapid response treatment in patients with MDD, met its primary endpoint and key secondary endpoint.

- **WATERFALL Study (completed)**

  In June 2021, we announced that the WATERFALL Study, a pivotal, Phase 3, double-blind, randomized, placebo-controlled clinical trial evaluating the efficacy and safety of zuranolone 50 mg in adults aged 18 to 64 years with MDD, met its primary endpoint.

- **SHORELINE Study (ongoing)**

  In March and December 2021, we reported positive topline 12-month data from both the 30 mg cohort and a portion of the 50 mg cohort of the SHORELINE Study, an open-label Phase 3 clinical trial of zuranolone in MDD, which is designed to evaluate the safety, tolerability, and need for repeat dosing of zuranolone in adults for up to one year. Enrollment in the 50 mg cohort of the study has been completed and the study is ongoing.

We are jointly developing zuranolone and another of our late-stage compounds, SAGE-324, in the U.S. with Biogen MA Inc., or BIMA, and Biogen International GmbH, or, together with BIMA, Biogen, under a collaboration and license agreement, or the Biogen Collaboration Agreement, that became effective in December 2020.

Under the Biogen Collaboration Agreement, we will also jointly commercialize products containing zuranolone, which we refer to as Licensed 217 Products, and products containing SAGE-324, which we refer to as Licensed 324 Products, with Biogen in the U.S. if our development efforts are successful. We refer to the Licensed 217 Products and Licensed 324 Products collectively as the Licensed Products. In addition, we have granted Biogen sole rights to develop and commercialize the Licensed Products outside the U.S., other than in Japan, Taiwan and South Korea, or the Shionogi Territory, with respect to zuranolone, where we have granted such rights to Shionogi & Co., Ltd., or Shionogi. We refer to the territories outside the U.S. to which Biogen has rights under the Biogen Collaboration Agreement with respect to the applicable Licensed Product as the Biogen Territory.

We also have a collaboration agreement with Shionogi for the development of zuranolone in the Shionogi Territory. In September 2021, Shionogi reported completion of a Phase 2 clinical trial of zuranolone for the treatment of patients with moderate to severe MDD in Japan, which Shionogi reported achieved its primary endpoints. Shionogi has also reported that it is conducting two Phase 3 trials of zuranolone for the treatment of patients with moderate to severe MDD as a monotherapy and as an add-on to other antidepressants, and announced that, pending results from these trials, it is aiming to submit an NDA to the Pharmaceuticals and Medical Devices Agency in Japan in the first quarter of 2024 seeking approval of zuranolone for the treatment of MDD.

SAGE-324 is a novel $GABA_A$ receptor positive allosteric modulator intended for chronic oral dosing. In April 2021, we and Biogen announced that our placebo-controlled Phase 2 KINETIC Study evaluating SAGE-324 for the treatment of adults with essential tremor had achieved its primary endpoint. We are currently enrolling patients with essential tremor in a Phase 2b dose-ranging clinical trial of SAGE-324, known as the KINETIC 2 Study. In May 2022, we also initiated an open-label Phase 2 clinical trial designed to evaluate the long-term safety and tolerability of SAGE-324 in patients with essential tremor, with incidence of treatment-emergent adverse events as the primary endpoint. This is intended to be a multi-year clinical trial, and will initially be open to rollover patients from other SAGE-324 clinical trials in patients with essential tremor, including the KINETIC 2 Study. We believe SAGE-324 also has potential for the treatment of a number

of other neurological conditions, including epilepsy and Parkinson's disease. Additional development plans for SAGE-324 will be determined as part of our strategic collaboration with Biogen.

Our second area of focus for development is novel compounds that target the NMDA receptor. Our lead product candidate selected in this area is SAGE-718, an oxysterol-based positive allosteric modulator of the NMDA receptor, which we are exploring in certain cognition-related disorders associated with NMDA receptor dysfunction, including cognition dysfunction associated with diseases such as Huntington's disease, Parkinson's disease and Alzheimer's disease.

The FDA has granted SAGE-718 Fast Track designation as a potential treatment for patients with Huntington's disease. SAGE-718 is currently being studied in three ongoing clinical trials in patients with Huntington's disease cognitive impairment:

- **DIMENSION Study**

  In February 2022, dosing commenced in the DIMENSION Study, a double-blind placebo-controlled Phase 2 clinical trial of SAGE-718 in patients with Huntington's disease cognitive impairment. The DIMENSION Study is designed to evaluate the efficacy of once-daily dosed SAGE-718 over three months.

- **SURVEYOR Study**

  In March 2022, we initiated the SURVEYOR Study, a placebo-controlled Phase 2 clinical trial of SAGE-718 in patients with Huntington's disease cognitive impairment, with a healthy volunteer component, with the goal of generating evidence linking efficacy signals on cognitive performance to domains of real-world functioning.

- **PURVIEW Study**

  In December 2022, we initiated the PURVIEW Study, a Phase 3 open-label study to evaluate the long-term safety and tolerability of SAGE-718 in patients with Huntington's disease cognitive impairment.

We are also evaluating SAGE-718 for the treatment of cognitive issues associated with Parkinson's disease and Alzheimer's disease. In May 2021, we announced results from the first part of a Phase 2a open-label study of SAGE-718 evaluating patients with mild cognitive impairment due to Parkinson's disease, known as the PARADIGM Study. Data from the PARADIGM Study showed that SAGE-718 had a positive impact on multiple domains of cognition, including executive function and learning and memory. As expected, no appreciable effect was observed on measures of simple attention or reaction time in keeping with the profile of SAGE-718 based on data to date. We have completed a four-week dosing cohort in the PARADIGM Study to gather additional data in the Parkinson's disease patient population and presented results in October 2022. In March 2022, we initiated a double-blind, placebo-controlled Phase 2 clinical trial of SAGE-718 in patients with mild cognitive impairment due to Parkinson's disease, known as the PRECEDENT Study. The PRECEDENT Study is designed to evaluate the safety and efficacy of SAGE-718 in patients with mild cognitive impairment due to Parkinson's disease over 42 days, followed by a controlled follow-up period.

In December 2021, we reported topline data from a Phase 2a open-label clinical trial of SAGE-718 in patients with mild cognitive impairment and mild dementia due to Alzheimer's disease, known as the LUMINARY Study. Data from the LUMINARY Study showed treatment with SAGE-718 resulted in consistent improvement across multiple tests of executive performance, as well as improvement on key tests of learning and memory. SAGE-718 has been well-tolerated in studies to date. In December 2022, we initiated the LIGHTWAVE Study, a randomized placebo-controlled Phase 2 clinical trial of SAGE-718 in patients with mild cognitive impairment and mild dementia due to Alzheimer's disease.

We have other programs at earlier stages of development with a focus on both acute and chronic brain health disorders. We expect to continue our work 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. We also believe that we may have the opportunity to use our scientific approach to explore targets beyond the $GABA_A$ and NMDA receptor systems and to develop compounds in areas of unmet need outside of brain health.

We began to generate revenue from product sales in the second quarter of 2019 in conjunction with the launch of our first product, ZULRESSO, in June 2019. In the fourth quarter of 2020, we recorded revenue from the strategic collaboration with and stock purchase by Biogen.

We have incurred net losses in each year since our inception, except for net income of $606.1 million for the year ended December 31, 2020, reflecting revenue recognized under the Biogen Collaboration Agreement, and we had an accumulated deficit of $2.0 billion as of December 31, 2022. Our net losses were $532.8 million and $457.9 million for the years ended December 31, 2022 and 2021, respectively. These losses have resulted principally from costs incurred in connection with research and development activities and selling, 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 in the foreseeable future in connection with our ongoing activities, including if and as we:

- continue our development efforts for zuranolone, including work to complete the open-label SHORELINE Study of zuranolone in MDD; advance our permitted pre-launch and launch-readiness activities with respect to zuranolone, and commercialize zuranolone in MDD and PPD, if approved; and potentially advance the development of zuranolone in additional indications as part of our strategic collaboration with Biogen;
- continue our commercialization efforts with respect to ZULRESSO for the treatment of PPD in the U.S., with a primary focus on geographies that have existing, active ZULRESSO treating sites;
- complete the ongoing and planned clinical trials of SAGE-324 as part of our strategic collaboration with Biogen;
- complete ongoing and planned clinical trials of SAGE-718;
- support our collaboration with Biogen with respect to zuranolone and SAGE-324 in the U.S., and support Biogen's development of zuranolone and SAGE-324 in Biogen's licensed territories outside the U.S. and Shionogi's development of zuranolone in the Shionogi Territory;
- advance our earlier-stage compounds;
- continue our research and development efforts to evaluate the potential for our existing product candidates for the treatment of additional indications or in new formulations;
- identify new targets, and generate and test new compounds and product candidates, with a focus on indications where we believe we can make well-informed, rapid go/no-go decisions, with the goal of developing a diversified portfolio of assets with differentiated features;
- prepare and file NDAs with the FDA and conduct permitted pre-launch activities with respect to any of our other product candidates that we believe have been successfully developed;
- commercialize any product candidates for which we obtain regulatory approval, including the manufacture of commercial supplies;
- continue to add personnel at the appropriate time, as our efforts and activities progress, including personnel to support ongoing zuranolone commercialization efforts, such as launch planning, permitted payor engagements, scientific exchange, disease awareness education, and ongoing product development, and to support launch of zuranolone in MDD and PPD, if approved;
- evaluate the market potential and regulatory pathways for our product candidates beyond zuranolone and SAGE-324 in the European Union and other jurisdictions outside the U.S., and determine how best to move forward where and when it may make business and strategic sense;
- continue to build, maintain, defend, leverage, and expand our intellectual property portfolio, including by utilizing 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; and

- continue to explore opportunities to establish licenses, collaborations or other agreements or alliances with other biotechnology and pharmaceutical companies, at the appropriate time, where we believe a collaboration will add significant value to our efforts, including through capabilities, infrastructure, speed or financial contributions, or to acquire new compounds, product candidates or products if we believe such opportunities will help us achieve our goals or meet other strategic objectives.

Until such time that we can generate significant revenue on a sustained basis from product sales and/or from collaborations, if ever, we expect to finance our operations primarily through a combination of revenue, equity or debt financings and other sources, including our collaborations with Biogen and Shionogi and potential future collaborations. We may not be successful in our commercialization of ZULRESSO, zuranolone, if approved, or any other product, and may not generate meaningful revenue or revenue at the levels or on the timing necessary to support our investment and goals. We may never successfully complete development of any of our current or future product candidates, successfully file for or obtain necessary regulatory approval for such product candidates, or achieve commercial viability for any resulting approved product. We may not obtain or maintain adequate patent protection or other exclusivity for our products or product candidates. Adequate additional financing may not be available to us on acceptable terms, or at all. Our inability to raise capital if and when needed would have a negative impact on our financial condition and on our ability to pursue our business strategy. Arrangements with our existing collaborators have required us to relinquish rights to certain of our technologies or product candidates, and any future collaborations may require us to relinquish additional rights. 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, 2022, in addition to anticipated funding from our ongoing collaborations, excluding revenues and milestones, will enable us to fund our operating expenses and capital expenditure requirements through 2024. See "—Liquidity and Capital Resources".

Financial Operations Overview

Revenue

We began to generate revenue from product sales in the second quarter of 2019 in conjunction with the launch of our first product, ZULRESSO as a treatment for PPD, in June 2019.

Our revenue from sales of ZULRESSO has been negatively impacted by significant barriers arising from the complex requirements for administration of the treatment and by the COVID-19 pandemic. ZULRESSO is administered as a continuous infusion given over two and a half days. Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness during the ZULRESSO infusion, ZULRESSO must be administered only in a medically-supervised healthcare setting that has been certified under a Risk Evaluation and Mitigation Strategies, or REMS, program and meets the other requirements of the REMS program, including requirements related to monitoring of the patient during the infusion. The actions required for a healthcare setting to be ready and willing to treat women with PPD are complex and time-consuming. These actions include: becoming REMS-certified; achieving formulary approvals; establishing protocols for administering ZULRESSO; and securing satisfactory reimbursement. Sites must often negotiate reimbursement on a payor-by-payor basis under commercial coverage. These requirements are expected to continue to limit future ZULRESSO revenue growth.

These barriers have been compounded by the COVID-19 pandemic, its related disruptive effects on the U.S. healthcare system, and other changes to the macroeconomic environment. The spread of COVID-19 in the U.S. resulted in a significant number of sites of care pausing, limiting or delaying treatment of new patients with ZULRESSO and potential new sites of care pausing site activation activities for a period of time. We believe that, at certain points during the pandemic, concerns about exposure to the virus or its variants caused a significant and sustained reduction in the number of women with PPD seeking treatment with ZULRESSO and in the number of physicians willing to prescribe it, and that difficulties in accessing treatment with ZULRESSO have since been compounded by healthcare staffing shortages and other changes to the macroeconomic environment. Given the ongoing disruption to the healthcare system in the U.S., including as a result of staffing shortages, we cannot predict for how long and to what extent ZULRESSO sales will be adversely impacted by these factors.

Our ZULRESSO commercial operations, including our account management field-based team and sales representatives, are primarily focused on geographies that have existing, active ZULRESSO treating sites. We expect that this approach to our commercial efforts will continue to substantially limit the revenue opportunity for ZULRESSO.

We expect that ZULRESSO revenues are likely to fluctuate quarter to quarter. We will not generate revenue from other products unless and until we or any of our collaborators successfully develop, obtain regulatory approval of, and commercialize one of our current or future product candidates. If we enter into additional collaboration agreements with third parties for our product candidates, we may generate revenue from those collaborations. We expect that revenue, if any, that we may generate under our existing or future collaboration agreements will fluctuate from quarter to quarter as a result of the timing and amount of license fees, payments for clinical materials or manufacturing services, milestone payments, royalties paid to us and our share of collaboration profits or losses resulting from sales of any commercialized products, and other payments.

In June 2018, we entered into a strategic collaboration with Shionogi for the clinical development and commercialization of zuranolone for the treatment of MDD and other potential indications in the Shionogi Territory. Under the terms of the agreement, Shionogi is responsible for all clinical development, regulatory filings and commercialization and manufacturing of zuranolone for MDD, and potentially other indications, in the Shionogi Territory. In October 2018, we also entered into a supply agreement with Shionogi under which we supply Shionogi with zuranolone clinical material. To date, revenue from our collaboration with Shionogi has come from an initial, upfront license fee upon execution of the collaboration agreement of $90.0 million, which was recorded as collaboration revenue in the year ended December 31, 2018, and for the supply of active pharmaceutical agreement, or API, for Shionogi's clinical trials.

In November 2020, we entered into the Biogen Collaboration Agreement with Biogen for the development, manufacture and commercialization of the Licensed Products. In connection with the execution of the Biogen Collaboration Agreement, we also entered into a stock purchase agreement for the sale and issuance to BIMA of

6,241,473 shares of our common stock for aggregate consideration of $650.0 million. The Biogen Collaboration Agreement became effective in December 2020, and the sale of the common stock under the stock purchase agreement closed on December 31, 2020. As a result of the purchase of common stock by BIMA, Biogen has become a related party of ours. Under the terms of the Biogen Collaboration Agreement, we will jointly develop and, if successful, jointly commercialize the Licensed Products in the U.S., and Biogen solely will develop and commercialize the Licensed Products in the Biogen Territory. We and Biogen have agreed to share equally all costs for activities, as well as the profits and losses, upon FDA approval of the Licensed Products, under the Biogen Collaboration Agreement solely for the U.S. Biogen is solely responsible for all costs for activities under the Biogen Collaboration Agreement in the Biogen Territory. Biogen will be the principal and record sales of SAGE-217 products globally. We will be the principal and record sales of SAGE-324 products in the U.S. and Biogen will record sales of SAGE-324 Products in the Biogen Territory. In the year ended December 31, 2020, we recorded collaboration revenue – related party of $1.1 billion, consisting of an upfront payment of $875.0 million plus $232.5 million in excess proceeds from the equity investment under the stock purchase agreement, when measured at fair value. For further discussion regarding the accounting for the Biogen Collaboration Agreement, refer to Note 6, *Collaboration Agreements,* in the accompanying Notes to Consolidated Financial Statements appearing elsewhere in this Annual Report.

Collaborative Arrangements

We analyze our collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and therefore within the scope of Accounting Standards Codification, or ASC, Topic 808, *Collaborative Arrangements*, or Topic 808. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of Topic 808 that contain multiple elements, we first determine which elements of the collaboration are deemed to be within the scope of Topic 808 and which elements of the collaboration are more reflective of a vendor-customer relationship and therefore within the scope of ASC Topic 606, *Revenue from Contracts with Customers*, or Topic 606. For elements of collaboration arrangements that are accounted for pursuant to Topic 808, an appropriate recognition method is determined and applied consistently, either by analogy to authoritative accounting literature or by applying a reasonable and rational policy election. For those elements of the arrangement that are accounted for pursuant to Topic 606, we apply the five-step revenue recognition model and present the arrangement as collaboration revenue in the consolidated statements of operations and comprehensive income (loss).

For collaboration arrangements that are within the scope of Topic 808, we evaluate the income statement classification for presentation of amounts due from or owed to other participants associated with multiple activities in a collaboration arrangement based on the nature of each separate activity. Payments or reimbursements that are the result of a collaborative relationship, instead of a customer relationship, such as co-development and co-commercialization activities, are recorded as research and development expense or selling, general and administrative expense in the event of a payment to the collaborative partner in a period, or a reduction to these expense line items in the event of a reimbursement from the collaboration partner in a period, as appropriate. For further discussion regarding the accounting for collaborative arrangements, refer to Note 6, *Collaboration Agreements,* in the accompanying Notes to Consolidated Financial Statements appearing elsewhere in this Annual Report.

Cost of Goods Sold

Cost of goods sold includes direct and indirect costs related to the manufacturing and distribution of ZULRESSO, including third-party manufacturing costs, packaging services, freight, third-party royalties payable on our net product revenue and amortization of intangible assets associated with ZULRESSO. Cost of goods sold may also include period costs related to certain inventory manufacturing services, inventory adjustment charges, as well as manufacturing variances. We estimate that our cost of goods sold as a percentage of net product revenue will remain in the high-single digit to low-double digits percentage range for the foreseeable future. We expect to utilize zero-cost inventory with respect to ZULRESSO for an extended period of time.

Operating Expenses

Our operating expenses consist primarily of costs associated with research and development activities and selling, 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 non-clinical studies and clinical trials and developing external manufacturing capabilities;
- costs of outside consultants engaged in research and development activities, including their fees and travel expenses;
- other expenses related to our non-clinical studies and clinical trials and expenses related to our regulatory activities, including the rolling NDA submission for zuranolone for the treatment of MDD and PPD which we completed in December 2022, as well as preparation for a potential FDA Advisory Committee meeting in connection with such filing;
- payments made under our third-party license agreements; and
- a portion of our information technology, facilities and other related expenses, including rent, depreciation, maintenance of facilities, insurance and supplies.

We consider the collaborative activities associated with the co-development, co-commercialization, and co-manufacturing of SAGE-217 products and SAGE-324 products in the U.S. to be separate units of account within the scope of Topic 808 as we and Biogen are both active participants in the development and commercialization activities and are exposed to significant risks and rewards that are dependent on the development and commercial success of the activities in the arrangement. Payments to or reimbursements from Biogen related to the co-development and co-manufacturing activities are accounted for as an increase to or reduction of research and development expense. During the years ended December 31, 2022 and 2021, we recorded net reimbursement of $73.2 million and $79.8 million, respectively, from Biogen that was deducted from our research and development expenses because we incurred a greater amount of these expenses than Biogen.

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, 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 or stock-based compensation in 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 results of ongoing, planned or future clinical trials and non-clinical studies;
- 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.

In addition, the COVID-19 pandemic and its downstream effects, such as healthcare and vendor staffing shortages and disruption to the U.S. healthcare system, and/or the impact of other macroeconomic and geopolitical conditions, may also negatively impact our ongoing and planned development activities and increase our research and development costs. Concerns, precautions and restrictions, staffing shortages, or other changes to the macroeconomic environment, or from continuing concerns about the COVID-19 pandemic, may substantially slow clinical site identification and activation and enrollment in our clinical trials, may impair or delay the conduct, auditing, monitoring, or completion of our trials, may impair or impede the timeliness and completion of our data collection and analysis efforts or the integrity of our data, or may cause us to pause trials, in each case which may significantly impact our ability to meet our expected timelines or cause us to change our plans and may significantly increase our research and development costs. For example, we have experienced slower than anticipated recruitment in certain clinical trials, including our ongoing KINETIC 2 Study of SAGE-324 in patients with essential tremor, for which we now expect to complete enrollment in late 2023, rather than in late 2022 as we had initially projected.

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.

Any failure to complete any stage of the development of any potential product candidates in a timely manner could have a material adverse effect on our operations, financial position and liquidity. A discussion of some of the risks and uncertainties associated with not completing our programs on schedule, or at all, and the potential consequences of failing to do so, are set forth in Part I, Item 1A of this Annual Report under the heading “Risk Factors”.

Selling, General and Administrative Expenses

Selling, general and administrative expenses consist primarily of personnel costs, including salaries, benefits and travel expenses for our executive, finance, business, commercial, corporate development and other administrative functions, and stock-based compensation expense. Selling, general and administrative expenses also include professional fees for expenses incurred under agreements with third parties relating to the commercialization of ZULRESSO; permitted pre-launch and launch-readiness activities related to zuranolone; public relations, audit, tax and legal services, including legal expenses to pursue patent protection of our intellectual property; and a portion of our information technology, facilities and other related expenses, including rent, depreciation, maintenance of facilities, insurance and supplies.

Our ongoing commercial efforts with respect to ZULRESSO, including our account management field-based team and sales representatives, are primarily focused on geographies that have existing, active ZULRESSO treating sites. We

expect to continue to incur significant commercialization expenses, including payroll and related expenses, to support our ongoing commercial activities associated with ZULRESSO. We expect that selling, general and administrative expenses will increase significantly in the future as we prepare for potential commercialization of zuranolone, engage in permitted pre-approval activities, recruit, train, and retain a direct sales force and commercialize zuranolone, if approved, and as we progress development efforts of our other current or future product candidates and commercialize those products, if successfully developed and approved. We expect to continue to incur significant expenses associated with general operations, including costs related to accounting and legal services, director and officer insurance premiums, facilities and other corporate infrastructure and office-related costs, such as information technology costs.

We consider the collaborative activities associated with the co-development, co-commercialization, and co-manufacturing of SAGE-217 products and SAGE-324 products in the U.S. to be separate units of account within the scope of Topic 808 as we and Biogen are both active participants in the development and commercialization activities and are exposed to significant risks and rewards that are dependent on the development and commercial success of the activities in the arrangement. Payments to or reimbursements from Biogen related to the co-commercialization activities are accounted for as an increase to or reduction of selling, general and administrative expense. During the years ended December 31, 2022 and 2021, we recorded net reimbursement of $2.2 million and $11.3 million, respectively, from Biogen that was deducted from our selling, general and administrative expenses because we incurred a greater amount of these expenses than Biogen.

Critical Accounting Policies and Significant Judgments and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the U.S. 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 Recognition

We generate revenue from the sale of ZULRESSO, which was approved by the FDA in March 2019 and we subsequently began selling in June 2019, and from collaboration and supply agreements with our collaborators. To date, revenue from collaboration agreements has come from initial, upfront payments allocated to licenses of intellectual property delivered to our collaborators and from the supply of material for clinical trials under a supply agreement.

Under ASC Topic 606, *Revenue from Contracts with Customers*, or Topic 606, an entity recognizes revenue when or as performance obligations are satisfied by transferring control of promised goods or services to a customer, 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(s) 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. 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.

For contracts determined to be within the scope of Topic 606, we assess whether the goods or services promised within each contract are distinct to identify those that are performance obligations. 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 and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract.

We allocate the transaction price (the amount of consideration we expect to be entitled to from a customer in exchange for the promised goods or services) to each performance obligation and recognize the associated revenue when (or as) each performance obligation is satisfied. Our estimate of the transaction price for each contract includes all variable consideration to which we expect to be entitled.

Collaboration and License Revenue

In assessing whether a promised good or service is distinct in the evaluation of a collaboration or license arrangement 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 we identify 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 standalone selling price 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, adjust our 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 estimate 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 arrangements with Shionogi and Biogen and concluded that a significant financing component does not exist for either arrangement. For arrangements with licenses of intellectual property that include sales-based royalties or milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties or milestone payments 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 or milestone payment 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. Revenue from our collaboration agreement with Shionogi has come from initial, upfront consideration upon execution of the agreement and for the supply of drug product for Shionogi clinical trials. Revenue from our collaboration agreement with Biogen has come from initial, upfront consideration related to the execution of the Biogen Collaboration Agreement. For additional information, refer to Note 6, *Collaboration Agreements*, to our consolidated financial statements appearing elsewhere in this Annual Report.

Product Revenue, Net

We recognize product revenues, net of variable consideration related to certain allowances and accruals that are determined using the expected value method, in our consolidated financial statements at the point in time when control transfers to the customer, which is typically when the product has been delivered to the customer's location. 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. Our only performance obligation identified for ZULRESSO is to deliver the product to the location specified by the customer's order. We record shipping and handling costs associated with delivery of product to our customers within selling, general and administrative expenses on our consolidated statements of operations and comprehensive income (loss). We expense incremental costs of obtaining a contract as incurred if the expected amortization period of the asset would be less than one year. If we were to incur incremental costs with an amortization period greater than a year, such costs would be capitalized as contract assets, as they are expected to be recovered, and would be expensed by amortizing on a systematic basis that is consistent with the transfer to the customer of the goods or services to which the asset relates. We did not have any contract assets (unbilled receivables) at December 31, 2022, as customer invoicing generally occurs before or at the time of revenue recognition. We did not have any contract liabilities at December 31, 2022, as we did not receive any payments in advance of satisfying our performance obligations to our customers. Amounts billed or invoiced that are considered trade accounts receivable are included in prepaid expenses and other current assets on the consolidated balance sheets. As of December 31, 2022 and 2021, the Company had not provided any allowance for bad debts against the trade accounts receivable, and the amount of trade accounts receivable was not significant.

We record reserves, based on contractual terms, for the following components of variable consideration related to product sold during the reporting period, as well as our estimate of product that remains in the distribution channel inventory of our customers at the end of the reporting period. On a quarterly basis, we update our estimates, if necessary, and record any material adjustments in the period they are identified.

Chargebacks: We estimate chargebacks from our customers who directly purchase the product from us for discounts resulting from contractual commitments to sell products to eligible healthcare settings at prices lower than the list prices charged to our customers. Customers charge us for the difference between what they pay to us for the product and the selling price to the eligible healthcare settings. Reserves for chargebacks consist of credits that we expect to issue for units that remain in the distribution channel inventories at the end of each reporting period that we expect will be sold to eligible healthcare settings, and chargebacks that customers have claimed, but for which we have not yet issued a credit.

Government Rebates: We are subject to discount obligations under government programs, including Medicaid. We record reserves for rebates in the same period the related product revenue is recognized, resulting in a reduction of ZULRESSO product revenue and a current liability that is included in accrued expenses on our consolidated balance sheets. Our liability for these rebates consists of invoices received for claims from prior quarters that have not been paid or for which an invoice has not yet been received, estimates of claims for the current quarter, and estimates of future claims that will be made for product that has been recognized as revenue, but which remains in the distribution channel at the end of each reporting period.

Trade Discounts and Allowances: We generally provide customary invoice discounts on ZULRESSO sales to our customers for prompt payment and we pay fees for sales order management, data, and distribution services. We estimate our customers will earn these discounts and fees and deduct these discounts and fees in full from gross ZULRESSO revenue and accounts receivable at the time we recognize the related revenue.

Financial Assistance: We provide voluntary financial assistance programs to patients with commercial insurance that have coverage and reside in states that allow financial assistance. We estimate the financial assistance amounts for ZULRESSO and record any such amounts within accrued expenses on the consolidated balance sheets. The calculation of the accrual for financial assistance is based on an estimate of claims and the cost per

claim that we expect to receive using demographics for patients who have registered and been approved for assistance. Any adjustments are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability, which is included as a component of accrued expenses on the consolidated balance sheets.

Product Returns: Consistent with industry practice, we offer product return rights to customers for damaged, defective or expiring product, provided it is within a specified period around the product expiration date as set forth in our return goods policy. We estimate the amount of our product sales that may be returned by our customers and record this estimate as a reduction of revenue in the period the related product revenue is recognized, as well as a reserve within accrued expenses on our consolidated balance sheets. Product returns have been not significant to date and are not expected to be significant in the future.

Collaborative Arrangements

We analyze our collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and therefore within the scope of ASC Topic 808, *Collaborative Arrangements*, or Topic 808. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of Topic 808 that contain multiple elements, we first determine which elements of the collaboration are deemed to be within the scope of Topic 808 and which elements of the collaboration are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606. For elements of collaboration arrangements that are accounted for pursuant to Topic 808, an appropriate recognition method is determined and applied consistently, either by analogy to authoritative accounting literature or by applying a reasonable and rational policy election. For those elements of the arrangement that are accounted for pursuant to Topic 606, we apply the five-step model described above and presents the arrangement as collaboration revenue in the consolidated statements of operations and comprehensive income (loss).

For collaboration arrangements that are within the scope of Topic 808, we evaluate the income statement classification for presentation of amounts due from or owed to other participants associated with multiple activities in a collaboration arrangement based on the nature of each separate activity. Payments or reimbursements that are the result of a collaborative relationship instead of a customer relationship, such as co-development and co-commercialization activities, are recorded as research and development expense or selling, general and administrative expense, in the event of a payment to the collaborative partner in a period, or a reduction to these expense line items in the event of a reimbursement from the collaboration partner in a period, as appropriate.

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 units, granted to employees, non-employee directors and non-employee consultants based on the estimated fair value on the date of grant, over the requisite service period. We recognize stock-based compensation expense for only the portion of awards that are expected to vest.

For awards that vest upon achievement of a performance condition, we recognize compensation expense when achievement of the performance condition is met or during the period from which meeting the condition is deemed probable until the expected date of meeting the performance condition, using management's best estimates, which consider the inherent risk and uncertainty regarding the future outcomes of the milestones.

The fair value of each stock option grant is estimated using the Black-Scholes option-pricing model. Effective January 1, 2020, we began using the historical volatility of only our common stock, as there is adequate historical data for the duration of the expected term.

The expected term of the stock options granted to employees, non-employee directors and non-employee consultants by us has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" stock options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the date of grant for time periods approximately equal to the expected term of the award. The expected dividend yield is zero, based on the fact that we have never paid cash dividends and do not expect to pay any cash dividends in the foreseeable future.

We also apply a forfeiture rate in order to calculate stock-based compensation expense. Expected forfeitures are based on our historical experience 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 fair value of each stock option granted under our equity plans has been calculated on the date of grant using the following weighted average assumptions:

	Year Ended December 31,		
	2022	2021	2020
Expected dividend yield	0%	0%	0%
Expected volatility	73%	76%	78%
Risk-free interest rate	2.49%	0.63%	0.97%
Expected term	6.03 years	5.92 years	5.98 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. In developing a forfeiture rate estimate for pre-vesting forfeitures, we have considered our historical experience of actual forfeitures. In the future, if our actual forfeiture rate is materially different from our estimate, then our stock-based compensation expense could be significantly different from what we have recognized in the current period.

As of December 31, 2022, we had unrecognized stock-based compensation expense related to our outstanding and unvested time-based stock option awards of $61.0 million, which is expected to be recognized over the remaining weighted average vesting period of 2.94 years.

As of December 31, 2022, 650,000 performance-based stock options were both outstanding and unvested, the total unrecognized stock-based compensation expense related to these awards was $8.2 million and the timing of recognition of this stock-based compensation expense is subject to our judgment as to when the performance conditions are considered probable of being achieved.

As of December 31, 2022, 160,403 time-based restricted stock units were both outstanding and unvested, and the total unrecognized stock-based compensation expense related to these awards was $5.0 million.

As of December 31, 2022, 1,255,078 performance restricted stock units were both outstanding and unvested, and the total unrecognized stock-based compensation expense related to these awards was $62.4 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, Summary of Significant Accounting Policies, to the consolidated financial statements appearing elsewhere in this Annual Report.

Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021:

	Year Ended December 31,		Increase (Decrease)
	2022	2021	
		(in thousands)	
Product revenue, net	$ 7,686	$ 6,308	$ 1,378
Operating costs and expenses:			
Cost of goods sold	813	553	260
Research and development	326,163	283,166	42,997
Selling, general and administrative	227,699	183,498	44,201
Total operating costs and expenses	554,675	467,217	87,458
Loss from operations	(546,989)	(460,909)	(86,080)
Interest income, net	14,190	2,883	11,307
Other income, net	15	134	(119)
Net loss	$ (532,784)	$ (457,892)	$ (74,892)

Product Revenue, Net

During the years ended December 31, 2022 and 2021, we recognized $7.7 million and $6.3 million, respectively, of net product revenue related to sales of ZULRESSO. Sales allowances and accruals consisted of chargebacks, discounts, distribution fees and patient financial assistance, and were not significant during either year.

Collaboration Revenue

During the years ended December 31, 2022 and 2021, we recognized no collaboration revenue from our agreement with Shionogi or collaboration revenue – related party from our agreement with Biogen.

We expect that revenue, if any, that we may generate under our collaboration agreements will fluctuate from quarter to quarter as a result of the timing and amount of license fees, payments for clinical materials or manufacturing services,

milestone payments, royalties paid to us and our share of collaboration profits or losses resulting from sales of any commercialized products, and other payments. We have the potential to receive milestone payments totaling $225.0 million related to the first commercial sale of zuranolone in MDD and PPD in the U.S., if zuranolone is approved for marketing. For further discussion regarding our collaboration agreements with Shionogi and Biogen and the accounting for revenue from collaboration agreements, refer to Note 2, *Summary of Significant Accounting Policies*; and Note 6, *Collaboration Agreements* in the Notes to Consolidated Financial Statements, appearing elsewhere in this Annual Report.

Cost of Goods Sold

During the years ended December 31, 2022 and 2021, cost of goods sold was $0.8 million and $0.6 million, respectively, and is made up of direct and indirect costs related to the manufacturing and distribution of ZULRESSO, including third-party manufacturing costs, packaging services, freight, third-party royalties payable on our net product revenue and amortization of intangible assets associated with ZULRESSO. Cost of goods sold may also include period costs related to certain inventory manufacturing services, inventory adjustment charges, as well as manufacturing variances. Prior to receiving initial FDA approval for ZULRESSO in March 2019, we manufactured ZULRESSO inventory to be sold upon commercialization and recorded $8.9 million related to this inventory build-up as research and development expense. As a result, the manufacturing costs related to the ZULRESSO inventory build-up incurred before FDA approval were already expensed in a prior period and are therefore excluded from the cost of goods sold for the years ended December 31, 2022 and 2021. We estimate that our cost of goods sold as a percentage of net product revenue will remain in the high-single digit to low-double digits percentage range for the foreseeable future. We expect to utilize zero-cost inventory with respect to ZULRESSO for an extended period of time.

Research and Development Expenses

The following table summarizes our research and development expenses for the years ended December 31, 2022 and 2021:

	Year Ended December 31,		Increase
	2022	2021	(Decrease)
	(in thousands)		
zuranolone (SAGE-217)	$ 93,440	$ 122,256	$ (28,816)
SAGE-324	31,496	18,771	12,725
SAGE-718	45,862	25,440	20,422
Other research and development programs	72,575	59,633	12,942
Unallocated expenses	130,129	87,168	42,961
Stock-based compensation	25,888	49,746	(23,858)
Net reimbursement from Biogen	(73,227)	(79,848)	6,621
	$ 326,163	$ 283,166	$ 42,997

Research and development expenses for the year ended December 31, 2022 were $326.2 million, compared to $283.2 million for the year ended December 31, 2021. The increase of $43.0 million was primarily due to the following:

- a decrease of $28.8 million in expenses for development of zuranolone, primarily due to completion of the WATERFALL Study and the CORAL Study;
- an increase of $12.7 million in expenses for development of SAGE-324, primarily due to activities directed towards the conduct of Phase 2 clinical trials which were initiated during 2021 and 2022;
- an increase of $20.4 million in expenses for development of SAGE-718, primarily due to activities directed towards the conduct of Phase 2 clinical trials which were initiated during 2021 and 2022;
- an increase of $12.9 million in expenses for other research and development programs, primarily due to increased work on early-stage research programs;
- an increase of $43.0 million in unallocated expenses, primarily due to an increase in the hiring of employees and corporate infrastructure costs, such as information technology costs, to support the growth in our operations;

- a decrease of $23.9 million in non-cash stock-based compensation expense. The decrease was primarily due to grants of stock options with high exercise prices that became fully vested before or during the year ended December 31, 2022, resulting in less expense than in the year ended December 31, 2021. The decrease was also due to the recognition of $9.8 million of expense related to performance-based vesting criteria during the year ended December 31, 2021. No expense was recognized related to the achievement of performance-based vesting criteria during the year ended December 31, 2022; and
- the net reimbursement from Biogen pursuant to the Biogen Collaboration Agreement decreased by $6.6 million. For the year ended December 31, 2022, the amount of net reimbursement was $46.4 million for zuranolone, $15.8 million for SAGE-324 and $11.0 million for costs that are reimbursable and included in unallocated expenses. For the year ended December 31, 2021, the amount of net reimbursement was $61.1 million for zuranolone, $9.4 million for SAGE-324 and $9.3 million for costs that are reimbursable and included in unallocated expenses. The primary reason for the decrease in net reimbursement was the increase in spending by Biogen for zuranolone.

Selling, General and Administrative Expenses

The following table summarizes our selling, general and administrative expenses for the years ended December 31, 2022 and 2021:

	Year Ended December 31,		Increase (Decrease)
	2022	2021	
		(in thousands)	
Personnel-related	$ 88,078	$ 52,100	$ 35,978
Stock-based compensation	35,714	54,883	(19,169)
Professional fees	56,833	43,428	13,405
Other	49,304	44,369	4,935
Net reimbursement from Biogen	(2,230)	(11,282)	9,052
	$ 227,699	$ 183,498	$ 44,201

Selling, general and administrative expenses for the year ended December 31, 2022 were $227.7 million, compared to $183.5 million for the year ended December 31, 2021. The increase of $44.2 million was primarily due to the following:

- an increase of $36.0 million in personnel-related costs, primarily due to hiring employees to support ongoing permitted pre-launch and launch-readiness activities with respect to zuranolone and in anticipation of a potential commercialization of zuranolone, if approved;
- a decrease of $19.2 million in non-cash stock-based compensation expense. The decrease was primarily due to grants of stock options with high exercise prices that became fully vested before or during the year ended December 31, 2022, resulting in less expense than in the year ended December 31, 2021. The decrease was also due to the recognition of $6.7 million of expense related to performance-based vesting criteria during the year ended December 31, 2021. No expense was recognized related to the achievement of performance-based vesting criteria during the year ended December 31, 2022;
- an increase of $13.4 million in professional fees, primarily due to permitted pre-launch and launch-readiness activities with respect to zuranolone;
- an increase in other expenses of $4.9 million, primarily due to an increase in corporate infrastructure costs, such as information technology costs, to support the growth in our operations; and

- the net reimbursement from Biogen pursuant to the Biogen Collaboration Agreement decreased by $9.1 million. For the year ended December 31, 2022, the amount of net reimbursement from Biogen to us was $3.6 million for external costs and the amount of net reimbursement from us to Biogen for personnel-related costs was $1.3 million. For the year ended December 31, 2021, the amount of net reimbursement from Biogen to us was $9.3 million for external costs and $2.0 million for personnel-related costs. The primary reason for the decrease in net reimbursement was an increase in the collaboration costs incurred by Biogen in anticipation of a potential commercialization of zuranolone, if approved.

Interest Income, Net and Other income, Net

Interest income, net, and other income, net, for the years ended December 31, 2022 and 2021 were $14.2 million and $3.0 million, respectively. The primary reason for the increase was the increase in interest rates.

Liquidity and Capital Resources

We began to generate revenue from product sales in the second quarter of 2019 in conjunction with the launch of our first product, ZULRESSO, in June 2019. We have incurred net losses in each year since our inception, except for net income of $606.1 million for the year ended December 31, 2020, reflecting revenue recognized under the Biogen Collaboration Agreement. As of December 31, 2022, we had an accumulated deficit of $2.0 billion. On December 31, 2020, we completed the sale of 6,241,473 shares of our common stock in a private placement to BIMA at a price of approximately $104.14 per share, resulting in aggregate gross proceeds of $650.0 million. From our inception through December 31, 2022, we have received aggregate net proceeds of $2.8 billion from the sales of redeemable convertible preferred stock prior to our initial public offering, the issuance of convertible notes, and the sales of common stock in our initial public offering in July 2014, follow-on offerings and in the sale of shares of our common stock to Biogen in connection with the Biogen Collaboration Agreement, which we refer to as the Biogen Equity Purchase. We also received $1.0 billion in upfront payments under our collaborations with Biogen and Shionogi.

As of December 31, 2022, our primary sources of liquidity were our cash, cash equivalents and marketable securities, which totaled $1.3 billion. We invest our cash in money market funds, U.S. government securities, corporate bonds, commercial paper, certificates of deposit and municipal securities, and our primary objectives are to preserve principal, provide liquidity and maximize income without significantly increasing risk.

The following table summarizes the primary sources and uses of cash for the years ended December 31, 2022 and 2021:

	Year Ended December 31,	
	2022	2021
	(in thousands)	
Net cash provided by (used in):		
Operating activities	$ (460,036)	$ (378,182)
Investing activities	325,433	(1,002,448)
Financing activities	3,070	13,334
	$ (131,533)	$ (1,367,296)

Operating Activities

During the year ended December 31, 2022, net cash used in operating activities primarily resulted from our net loss of $532.8 million, which was primarily attributable to our research and development activities and our selling, general and administrative expenses, along with changes in our operating assets and liabilities of $5.7 million, partially offset by $67.1 million of non-cash items.

During the year ended December 31, 2021, net cash used in operating activities primarily resulted from our net loss of $457.9 million, which was primarily attributable to our research and development activities and our selling, general and administrative expenses, along with changes in our operating assets and liabilities of $18.5 million, partially offset by $98.2 million of non-cash items.

Investing Activities

During the years ended December 31, 2022 and 2021, net cash provided by investing activities was $325.4 million and net cash used by investing activities was $1.0 billion, respectively. During the years ended December 31, 2022 and 2021, we purchased marketable securities and had sales and maturities of our marketable securities as part of managing our cash and investments portfolio. Additionally, during the year ended December 31, 2021, we invested the majority of the cash that we received from Biogen under the Biogen Collaboration Agreement and the Biogen Equity Purchase in marketable securities.

Financing Activities

During the years ended December 31, 2022 and 2021, net cash provided by financing activities was $3.1 million and $13.3 million, respectively. The decrease was mainly due to a decrease of proceeds from the exercises of stock options.

Operating Capital Requirements

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 our current and future product candidates, and seek regulatory approvals for zuranolone and those other product candidates that are successfully developed; prepare for potential future commercialization of zuranolone and other product candidates beyond ZULRESSO that are successfully developed and approved, including engaging in pre-launch and launch-readiness activities; begin to commercialize any such products, if approved; and continue our efforts to identify and develop new product candidates beyond our current portfolio. We also expect to incur significant costs associated with general operations. In addition, we expect to incur significant commercialization expenses for product sales, marketing and outsourced manufacturing with respect to ZULRESSO, zuranolone, if approved and any other future products that are successfully developed and approved. Accordingly, we anticipate that we will need substantial additional funding in connection with our continuing operations.

We expect that our existing cash, cash equivalents and marketable securities as of December 31, 2022, in addition to anticipated funding from our ongoing collaborations, excluding revenues and milestones, will enable us to fund our operating expenses and capital expenditure requirements through 2024. During that time, we expect research and development and selling, general and administrative expenses to increase as we advance planned and ongoing clinical trials for SAGE-718 and SAGE-324; advance regulatory, engage in permitted pre-launch and launch-planning activities for zuranolone; prepare for the potential commercial launch of zuranolone; expand our research activities; and pursue our strategic plan.

Our current operating plan does not contemplate other 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, commercialization or other efforts. Because of the numerous risks and uncertainties associated with the development and commercialization of any product or product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenditures necessary to complete development of our current or future product candidates or to commercialize any approved product.

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

- our ability to successfully receive FDA approval of our NDA to market zuranolone for the treatment of MDD and PPD, on the timelines we expect;
- the costs of regulatory, permitted pre-launch and launch-readiness activities associated with zuranolone;
- if zuranolone is approved for one or more indications, the costs associated with its commercial launch and the timing and amount of any revenues;

- the timing and amount of revenues from sales of ZULRESSO, which we expect will continue to be impacted by a number of factors, including: the rate, degree and level of market acceptance for ZULRESSO for the treatment of PPD in the U.S.; our decision to focus our efforts primarily on geographies that have existing, active ZULRESSO treating sites; the continued availability of healthcare settings in those geographies to administer ZULRESSO and the ability and willingness of such healthcare settings to make sufficient capacity available, particularly in light of the ongoing disruption to the U.S. healthcare system and related healthcare staffing shortages stemming from the downstream effects of the COVID-19 pandemic; the level of reimbursement for both ZULRESSO and the infusion in the healthcare setting both by commercial and government payors, and the nature of limitations on coverage and reimbursement; the number of healthcare professionals willing to prescribe ZULRESSO and women with PPD who agree to be treated with ZULRESSO; and the scope, duration and timing of the impact of the COVID-19 pandemic and its downstream effects;
- the timing and amount of costs associated with our commercialization of ZULRESSO;
- the initiation, progress, completion, timing, costs, and results of ongoing, planned and future non-clinical studies and clinical trials for our other 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, submitting and supporting regulatory filings for our product candidates;
- the length, severity and costs of downstream disruptions and other changes to the macroeconomic environment as a result of the COVID-19 pandemic, including any capacity and resource constraints at our vendors and clinical trial sites on initiation and conduct of our clinical trials or on our supply chain;
- the ability of SAGE-324, SAGE-718 and our other clinical-stage product candidates to progress through clinical development successfully and on the timelines we expect; the outcome of discussions with regulatory authorities on regulatory pathways with respect to our product candidates; the timing, scope and outcome of regulatory filings and 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 resulting from such development efforts, if successful; and the level, timing and amount of costs associated with permitted prelaunch activities and preparing for a potential future commercial launch of any such product candidate that is successfully developed and approved;
- the amounts we are entitled to receive, if any, from Biogen and Shionogi under our collaborations for profit-sharing, cost-sharing, development, regulatory, and sales milestones, and royalty payments;
- the size of the markets for which zuranolone and our other product candidates may be approved in the future, if successfully developed; the portion of the population in the approved indications for which zuranolone, if approved, and our future products are actually prescribed; and the rate and degree of market acceptance, pricing, and availability and level of reimbursement for zuranolone, if approved, and for our future products, if successfully developed and approved;
- 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/or collaboration revenue and achieve sustained profitability, we expect to also 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 other 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, licensing arrangements or other agreements 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. Raising funds may present challenges. Markets may experience volatility or become disrupted in the future for any number of reasons, including if the long-term negative effects of the COVID-19 pandemic, even after the pandemic has subsided, or other macroeconomic or geopolitical conditions, result in an economic recession, a decrease in corporate and consumer expenditures, prolonged unemployment, or other circumstances that could negatively impact general economic conditions. 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, 2022 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]	$ 12,959	$ 7,643	$ 5,316	$ —	$ —
Total[1][2][3]	$ 12,959	$ 7,643	$ 5,316	$	$ —

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, 2022, of 63,017 square feet in the first building under an operating lease, as amended, that will expire on August 31, 2024 and 40,419 square feet in the second building under an operating lease, as amended, that will expire on August 31, 2024. We lease office space in a multi-tenant building in Raleigh, North Carolina, consisting of 15,525 square feet under an operating lease that will expire on November 30, 2024. We may 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. 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 $23.8 million upon achieving certain milestones, related to clinical development, regulatory approvals and sales. During the year ended December 31, 2022, we recorded no expense for milestones 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.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We had cash, cash equivalents and marketable securities of $1.3 billion as of December 31, 2022. 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 do not expect that a sudden change in market interest rates would 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 that are in excess of federally insured limits at one or more financial institutions.

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, 2022.

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 (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Securities Exchange Act of 1934) 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 our 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, 2022, 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. 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, 2022, 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, 2022 and concluded that it was effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2022 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 (as defined in Rules 13a-15(f) and 15d-15(f) under the Securities Exchange Act of 1934) that occurred during the quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

Not applicable.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item is incorporated herein by reference to the information that will be contained in "Election of Directors" and "Corporate Governance" in our proxy statement related to the 2023 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.

Code of Business Conduct and Ethics. We have adopted a Code of Business Conduct and Ethics, which we call our Values Code, that applies to all of our employees, officers and directors, including those officers responsible for financial reporting. The current version of the Values Code, as may be amended from time to time, is available on our website at http://investor.sagerx.com/corporate-governance. A copy of the Values Code may also be obtained, free of charge, upon a request directed to: Sage Therapeutics, Inc., 215 First Street, Cambridge, Massachusetts 02142, Attention: SVP, General Counsel. We intend to disclose any amendment or waiver of a provision of the Values Code that applies to our principal executive officer, principal financial officer, or principal accounting officer, or persons performing similar functions, by posting such information on our website (available at www.sagerx.com) and/or in our public filings with the Securities and Exchange Commission.

Item 11. Executive Compensation

The information required by this Item is incorporated herein by reference to the information that will be contained in "Executive Officer and Director Compensation," "Compensation Committee Interlocks and Insider Participation" and "Compensation Committee Report," but exclusive of any information contained under the heading "Pay Versus Performance" in our proxy statement related to the 2023 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 "Securities Authorized for Issuance Under Equity Compensation Plans" and "Security Ownership of Certain Beneficial Owners and Management" in our proxy statement related to the 2023 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 "Corporate Governance" and "Certain Relationships and Related Party Transactions" in our proxy statement related to the 2023 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 "Ratification of Appointment of Auditors" in our proxy statement related to the 2023 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 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, 2022 and 2021, and the related consolidated statements of operations and comprehensive income (loss), of changes in stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2022, 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, 2022, 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, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022 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, 2022, 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 Management's Report on Internal Control over Financial Reporting appearing under Item 9A. 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.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued Research and Development Costs

As described in Notes 2 and 4 to the consolidated financial statements, the Company has entered into various research and development contracts with research institutions and other companies. When billing terms under these contracts do not coincide with the timing of when the work is performed, management is required to make estimates of outstanding obligations to those third parties as of the end of the reporting period. Within accrued expenses, total accrued research and development costs amounted to $32.6 million as of December 31, 2022, which include accruals for these estimated ongoing research and development costs. Any accrual estimates are based on a number of factors, including management's knowledge of the progress towards completion of the research and development activities, invoicing to date under the contracts, communication from the research institution or other companies of any actual costs incurred during the period that have not yet been invoiced, and the costs included in the contracts. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period.

The principal considerations for our determination that performing procedures relating to accrued research and development costs is a critical audit matter are the significant judgment by management in determining the accrued costs which in turn led to a high degree of auditor judgment, subjectivity and effort in performing procedures and evaluating audit evidence for these accrued costs and the factors related to progress towards completion of the research and development activities, invoicing to date under the contracts, and communication from the research institution or other companies of any actual costs incurred during the period that have not yet been invoiced.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls relating to accrued research and development costs, including controls over the review of contracts, accumulating information on actual costs incurred during the period, and assessment of progress towards completion of the research and development activities. These procedures also included, among others, (i) testing management's process for estimating accrued research and development costs; (ii) evaluating the appropriateness of the method used by management to develop the estimates; (iii) evaluating the reasonableness of the factors used in determining the estimates related to progress towards completion of specific research and development activities and the associated cost incurred for services the Company has not yet been invoiced or otherwise notified of the actual cost at period end; and (iv) testing the completeness and accuracy of the underlying data including total costs included within executed contracts and actual billed expenses under these contracts.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
February 16, 2023

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, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 162,700	$ 294,233
Marketable securities	1,109,794	1,448,063
Prepaid expenses and other current assets	50,826	39,841
Collaboration receivable - related party	13,660	18,506
Total current assets	1,336,980	1,800,643
Property and equipment, net	2,898	3,016
Restricted cash	1,269	1,269
Right-of-use operating asset	10,532	16,109
Other long-term assets	4,770	4,251
Total assets	$ 1,356,449	$ 1,825,288
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 18,950	$ 10,450
Accrued expenses	72,666	67,275
Operating lease liability, current portion	7,643	7,468
Total current liabilities	99,259	85,193
Operating lease liability, net of current portion	4,491	10,964
Other liabilities	100	100
Total liabilities	103,850	96,257
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, $0.0001 par value per share; 5,000,000 shares authorized at December 31, 2022 and December 31, 2021; no shares issued or outstanding at December 31, 2022 and December 31, 2021	—	—
Common stock, $0.0001 par value per share; 120,000,000 shares authorized at December 31, 2022 and December 31, 2021; 59,512,158 and 58,940,083 shares issued at December 31, 2022 and December 31, 2021; 59,509,125 and 58,937,050 shares outstanding at December 31, 2022 and December 31, 2021	6	6
Treasury stock, at cost, 3,033 shares at December 31, 2022 and December 31, 2021	(400)	(400)
Additional paid-in capital	3,291,369	3,227,471
Accumulated deficit	(2,028,170)	(1,495,386)
Accumulated other comprehensive loss	(10,206)	(2,660)
Total stockholders' equity	1,252,599	1,729,031
Total liabilities and stockholders' equity	$ 1,356,449	$ 1,825,288

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

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

	Year Ended December 31,		
	2022	2021	2020
Product revenue, net	$ 7,686	$ 6,308	$ 6,700
Collaboration revenue - related party	—	—	1,107,500
Total revenue	7,686	6,308	1,114,200
Operating costs and expenses:			
Cost of goods sold	813	553	565
Research and development	326,163	283,166	292,714
Selling, general and administrative	227,699	183,498	196,952
Restructuring	—	—	27,743
Total operating costs and expenses	554,675	467,217	517,974
Income (loss) from operations	(546,989)	(460,909)	596,226
Interest income, net	14,190	2,883	9,597
Other income, net	15	134	250
Net income (loss)	$ (532,784)	$ (457,892)	$ 606,073
Net income (loss) per share—basic	$ (8.98)	$ (7.80)	$ 11.66
Net income (loss) per share—diluted	$ (8.98)	$ (7.80)	$ 11.43
Weighted average number of common shares outstanding—basic	59,306,094	58,670,230	51,983,188
Weighted average number of common shares outstanding—diluted	59,306,094	58,670,230	53,003,115
Comprehensive income (loss):			
Net income (loss)	$ (532,784)	$ (457,892)	$ 606,073
Other comprehensive items:			
Unrealized loss on marketable securities	(7,546)	(3,075)	(880)
Total other comprehensive loss	(7,546)	(3,075)	(880)
Total comprehensive income (loss)	$ (540,330)	$ (460,967)	$ 605,193

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 Capital	Accumulated Other Comprehensive Gain (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount	Shares	Amount				
Balances at December 31, 2019	51,877,194	$ 5	3,033	$ (400)	$ 2,587,322	$ 1,295	$ (1,643,567)	$ 944,655
Issuance of common stock from exercises of stock options	117,025	—	—	—	5,082	—	—	5,082
Issuance of common stock under the employee stock purchase plan	72,719	—	—	—	4,936	—	—	4,936
Stock-based compensation expense	—	—	—	—	94,968	—	—	94,968
Issuance of common stock under the Stock Purchase Agreement - related party	6,241,473	1	—	—	417,499	—	—	417,500
Change in unrealized loss on available-for-sale securities	—	—	—	—	—	(880)	—	(880)
Net income	—	—	—	—	—	—	606,073	606,073
Balances at December 31, 2020	58,308,411	6	3,033	(400)	3,109,807	415	(1,037,494)	2,072,334
Issuance of common stock from exercises of stock options	307,378	—	—	—	12,397	—	—	12,397
Issuance of common stock under the employee stock purchase plan	46,759	—	—	—	2,761	—	—	2,761
Stock-based compensation expense	—	—	—	—	103,891	—	—	103,891
Vesting of restricted stock units, net of employee tax obligations	274,502	—	—	—	(1,385)	—	—	(1,385)
Change in unrealized loss on available-for-sale securities	—	—	—	—	—	(3,075)	—	(3,075)
Net loss	—	—	—	—	—	—	(457,892)	(457,892)
Balances at December 31, 2021	58,937,050	6	3,033	(400)	3,227,471	(2,660)	(1,495,386)	1,729,031
Issuance of common stock from exercises of stock options	150,045	—	—	—	1,037	—	—	1,037
Issuance of common stock under the employee stock purchase plan	57,239	—	—	—	2,346	—	—	2,346
Stock-based compensation expense	—	—	—	—	60,558	—	—	60,558
Vesting of restricted stock units, net of employee tax obligations	364,791	—	—	—	(43)	—	—	(43)
Change in unrealized loss on available-for-sale securities	—	—	—	—	—	(7,546)	—	(7,546)
Net loss	—	—	—	—	—	—	(532,784)	(532,784)
Balances at December 31, 2022	59,509,125	$ 6	3,033	$ (400)	$ 3,291,369	$ (10,206)	$ (2,028,170)	$ 1,252,599

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,		
	2022	2021	2020
Cash flows from operating activities			
Net income (loss)	$ (532,784)	$ (457,892)	$ 606,073
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Stock-based compensation expense	61,602	104,629	95,994
Premium on marketable securities	(1,500)	(23,641)	(1,736)
Amortization of premium on marketable securities	5,853	13,046	1,048
Depreciation expense	1,122	4,182	2,630
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(10,985)	(17,020)	3,879
Collaboration receivable - related party	4,846	(18,506)	—
Other long-term assets	(519)	(910)	452
Right-of-use operating asset	5,577	5,221	6,397
Operating lease liabilities, current	175	206	36
Operating lease liabilities, non-current	(6,473)	(5,944)	(6,825)
Accounts payable	8,433	6,689	(11,511)
Accrued expenses and other liabilities	4,617	11,758	(32,157)
Net cash provided by (used in) operating activities	(460,036)	(378,182)	664,280
Cash flows from investing activities			
Proceeds from sales and maturities of marketable securities	1,207,407	988,075	901,749
Purchases of marketable securities	(881,037)	(1,990,151)	(458,720)
Purchases of property and equipment	(937)	(372)	(345)
Net cash provided by (used in) investing activities	325,433	(1,002,448)	442,684
Cash flows from financing activities			
Proceeds from stock option exercises and employee stock purchase plan issuances	3,113	14,719	9,262
Payment of employee tax obligations related to vesting of restricted stock units	(43)	(1,385)	—
Proceeds from the sale of common stock under the Stock Purchase Agreement - related party	—	—	417,500
Net cash provided by financing activities	3,070	13,334	426,762
Net increase (decrease) in cash, cash equivalents and restricted cash	(131,533)	(1,367,296)	1,533,726
Cash, cash equivalents and restricted cash at beginning of period	295,502	1,662,798	129,072
Cash, cash equivalents and restricted cash at end of period	$ 163,969	$ 295,502	$ 1,662,798
Supplemental disclosure of non-cash operating and investing activities			
Purchases of property and equipment included in accounts payable	$ 137	$ 70	$ —
Lease asset de-recognized upon lease cancellation	$ —	$ 3,733	$ 2,310

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

1. Nature of the Business

Sage Therapeutics, Inc. ("Sage" or the "Company") is a biopharmaceutical company with a mission to pioneer solutions to deliver life-changing brain health medicines, so every person can thrive.

The Company's first product, ZULRESSO® (brexanolone) CIV injection, is approved in the U.S. as a treatment for postpartum depression ("PPD") in adults. The Company launched ZULRESSO commercially in the U.S. in June 2019. The Company's submission of a new drug application (an "NDA") for its lead investigational product candidate, zuranolone, for the treatment of major depressive disorder ("MDD") and PPD was accepted for filing and granted priority review by the U.S. Food and Drug Administration ("FDA") in February 2023. The Company has a portfolio of other product candidates with a current focus on modulating two critical central nervous system ("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 currently targeting diseases and disorders of the brain with three key focus areas: depression, neurology and neuropsychiatry.

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.

Risks and Uncertainties

The Company is subject to risks and uncertainties common to companies in the biotechnology and pharmaceutical industries, 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 the marketing and sale of pharmaceutical products; the potential for development by third parties of new technological innovations that may compete with the Company's products and product candidates; the dependence on key personnel; the challenges of protecting proprietary technology; the need to comply with government regulations; the high costs of drug development; the uncertainty of being able to secure additional capital when needed to fund operations; and the direct or indirect impact of the COVID-19 pandemic on its development activities, operations and financial condition.

The product candidates developed by the Company require approvals from the FDA 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, or that the Company's current product, ZULRESSO, will maintain, 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 for any of its product candidates, including zuranolone, such occurrences may have a material adverse impact on the Company's business and its financial condition.

The Company is also subject to additional risks and uncertainties related to the ongoing COVID-19 pandemic and other macroeconomic and geopolitical events, which collectively have caused and may continue to cause major disruptions to businesses and economies worldwide.

The rapid spread of COVID-19 in the U.S. resulted in a significant reduction in patient demand for ZULRESSO and in the number of sites available to administer ZULRESSO at certain points during the pandemic. There have been and continue to be healthcare staffing shortages and other changes to the macroeconomic environment as downstream effects of the pandemic have continued. These factors have had a significant and sustained negative impact on the Company's revenue from sales of ZULRESSO. While the Company has not experienced any other material disruptions to date as a result of the COVID-19 pandemic, any prolonged material disruptions to the work of the Company's employees,

suppliers, contract manufacturers, or vendors could negatively impact the Company's activities, availability of supplies, or operating results. In addition, while the Company has seen slower patient recruitment in certain clinical trials due to the COVID-19 pandemic and its downstream effects, and has experienced some challenges in qualifying and activating clinical trial sites, including due to capacity and resource constraints and employee attrition at our vendors and at sites, the Company has not experienced other significant impacts to the Company's development activities as a result of the COVID-19 pandemic. Any material disruption to the Company's development activities may cause delays, increase the Company's costs and impact the Company's operating results. In addition, the COVID-19 pandemic initially caused major volatility in capital markets and a significant global economic downturn, and the Company's ability to access the capital markets in the future could be negatively impacted if there are long-term negative effects of the COVID-19 pandemic on the macroeconomic environment or capital markets.

Moreover, U.S. and global financial markets have experienced volatility and disruption due to other macroeconomic and geopolitical events such as rising inflation, the risk of a recession and the ongoing conflict between Russia and Ukraine. The Company cannot predict at this time to what extent it and its collaborators, employees, suppliers, contract manufacturers and/or vendors could potentially be negatively impacted by these events.

Going Concern

Under Accounting Standards Update ("ASU") No. 2014-15, *Presentation of Financial Statements—Going Concern* (Subtopic 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 in each year since its inception, except for net income of $606.1 million for the year ended December 31, 2020, reflecting revenue recognized under a collaboration and license agreement with Biogen MA Inc. ("BIMA") and Biogen International GmbH (collectively with BIMA, "Biogen") (the "Biogen Collaboration Agreement"). As of December 31, 2022, the Company had an accumulated deficit of $2.0 billion. From its inception through December 31, 2022, the Company has received aggregate net proceeds of $2.8 billion from the sales of redeemable convertible preferred stock prior to its initial public offering ("IPO"), the issuance of convertible notes, and the sales of common stock in its IPO in July 2014, in follow-on public offerings and to BIMA under a stock purchase agreement executed in connection with the Biogen Collaboration Agreement. The Company has also received $1.0 billion in upfront payments under its collaborations with Biogen and Shionogi & Co., Ltd. ("Shionogi"). Until such time, if ever, as the Company can generate substantial product revenue and/or collaboration revenue and achieve sustained 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 or other sources of funding 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 currently planned operations for at least the next 12 months from the filing date of this Annual Report. At some point after that time, the Company anticipates it will require additional financing to fund its future operations. Even if the Company believes it has sufficient funds for its current or future operating plans, the Company may seek to raise additional capital if market conditions are favorable or in light of other strategic considerations.

2. Summary of Significant Accounting Policies

The following is a summary of significant accounting policies followed in the preparation of these consolidated 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 U.S. ("GAAP").

Principles of Consolidation

The consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries. Intercompany accounts and transactions have been eliminated.

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. The full extent to which the COVID-19 pandemic and its downstream effects may directly or indirectly impact the Company's business, results of operations and financial condition, including sales, expenses, reserves and allowances, manufacturing, clinical trials, research and development costs and employee-related amounts, will depend in large part on future developments, which cannot be predicted with confidence at this time, including: the scope, duration and severity of ongoing and future waves of the pandemic, including the impact of any variant strains of the COVID-19 virus; the extent of healthcare staffing shortages that have continued even as COVID-19 related restrictions have eased; the impact of the pandemic on the Company's customers and vendors, including capacity and resource constraints; the impact of the downstream effects of the pandemic on business operations across the U.S.; and the scope and extent of any future actions or restrictive measures taken to contain or mitigate the impact of the pandemic. The Company has made estimates of the impact of the COVID-19 pandemic within its consolidated financial statements. Due to the evolving nature of the COVID-19 pandemic, its downstream effects, and their impacts, there may be changes to those estimates in future periods, and actual results could differ from those estimates.

Cash Equivalents

The Company considers all highly liquid investments with an original maturity of 90 days or less to be cash equivalents. As of December 31, 2022, cash equivalents were comprised of money market funds. As of December 31, 2021, cash equivalents were comprised of money market funds, U.S. commercial paper and international commercial paper.

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 marketable securities 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 the accumulated other comprehensive items in stockholders' equity. When the fair value is below the amortized cost of the asset, an estimate of expected credit losses is made. The credit-related impairment amount is recognized in net income (loss); the remaining impairment amount and unrealized gains are reported as a component of accumulated other comprehensive items in stockholders' equity. Credit losses are recognized through the use of an allowance for credit losses account and subsequent improvements in expected credit losses are recognized as a reversal of an amount in the allowance for credit losses account. If the Company has the intent to sell the security or it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis, then the allowance for the credit loss is written-off and the excess of the amortized cost basis of the asset over its fair value is recorded in the consolidated statements of operations and comprehensive income (loss). Regardless of the Company's intent to sell a security, it performs additional analysis on all securities with unrealized losses to evaluate losses associated with the creditworthiness

of the security. Credit losses are identified where the Company does not expect to receive cash flows sufficient to recover the amortized cost basis of a security.

Accounts Receivable

The Company's trade accounts receivable consist of amounts due from specialty distributors, specialty pharmacies, and medically-supervised healthcare settings that have been certified under a Risk Evaluation and Mitigation Strategy ("REMS") program in the U.S. related to sales of ZULRESSO and have standard payment terms that generally require payment within 30 to 90 days from the invoice date. The Company monitors the financial performance and creditworthiness of customers so that it can properly assess and respond to changes in their credit profiles. The Company makes judgments as to its ability to collect outstanding receivables and provides an allowance for bad debts against the trade account receivables, when appropriate. As of December 31, 2022 and 2021, trade accounts receivable were $1.5 million and $1.1 million, respectively, and are included in prepaid expenses and other current assets on the consolidated balance sheets. As of December 31, 2022, the Company has not provided any allowance for bad debts against the trade accounts receivable.

Inventory

Prior to the initial date that regulatory approval is received for a product candidate of the Company, costs related to the production of inventory are recorded as research and development expense on the Company's consolidated statements of operations and comprehensive income (loss) in the period incurred. In connection with the FDA approval of ZULRESSO in March 2019, the Company subsequently began capitalizing inventory manufactured or purchased after this date.

Inventory is stated at the lower of cost or estimated net realizable value with cost determined on a first-in, first-out basis. Inventory costs include raw materials, third-party contract manufacturing, third-party packaging services, and freight. Raw and intermediate materials that may be utilized for either research and development or commercial purposes, after approval of the product by the FDA, are classified as inventory. Amounts in inventory that are used for research and development purposes are charged to research and development expense when the product enters the research and development process and can no longer be used for commercial purposes and, therefore, does not have an "alternative future use" as defined in authoritative guidance. The Company performs an assessment of the recoverability of capitalized inventory during each reporting period and, if needed, writes down any excess and obsolete inventory to its estimated net realizable value in the period it is identified. If they occur, such impairment charges are recorded as a component of cost of goods sold in the consolidated statements of operations and comprehensive income (loss). As of December 31, 2022 and 2021, inventory was $1.7 million and $1.4 million, respectively, and are included in prepaid expenses and other current assets on the consolidated balance sheets.

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 the Company's consolidated statements of operations and comprehensive income (loss). Repairs and maintenance costs are expensed as incurred.

Leases

The Company determines if an arrangement is a lease at contract inception. Operating lease assets represent the Company's right to use an underlying asset for the lease term and operating lease liabilities represent the Company's obligation to make payments arising from the lease. Operating lease assets and liabilities are recognized at the commencement date of the lease based upon the present value of lease payments over the lease term. When determining the lease term, the Company includes options to extend or terminate the lease when it is reasonably certain that the Company will exercise those options. The Company uses the Company's incremental borrowing rate when the implicit interest rate is not readily determinable based upon the information available at the commencement date of the lease in determining the present value of the lease payments and the implicit interest rate when readily determinable.

The lease payments used to determine the Company's operating lease assets may include lease incentives, stated rent increases and escalation clauses linked to rates of inflation, when determinable, and are recognized in the Company's operating lease assets in the Company's consolidated balance sheets. In addition, the Company's contracts may contain lease and non-lease components. The Company combines lease and non-lease components, which are accounted for together as lease components.

The Company's operating leases are reflected in the right-of-use operating asset; operating lease liability, current portion; and operating lease liability, net of current portion in the Company's consolidated balance sheets. Lease expense for minimum lease payments is recognized on a straight-line basis over the lease term. Short-term leases, defined as leases that have a lease term of 12 months or less at the commencement date, are not recorded on the Company's consolidated balance sheets and are recognized in the consolidated statements of operations and comprehensive income (loss) on a straight-line basis over the term of the lease.

Variable lease payments are the amounts owed by the Company to a lessor that are not fixed, such as reimbursement for common area maintenance and utilities costs for facility leases. Variable lease payments are expensed when 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. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. 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.

Cost of Goods Sold

Cost of goods sold includes direct and indirect costs related to the manufacturing and distribution of ZULRESSO, including third-party manufacturing costs, packaging services, freight, third-party royalties payable on the Company's net product revenue and amortization of intangible assets associated with ZULRESSO. Cost of goods sold may also include period costs related to certain inventory manufacturing services, inventory adjustment charges, as well as manufacturing variances. In connection with the FDA approval of ZULRESSO in March 2019, the Company subsequently began capitalizing inventory manufactured or purchased after this date. As a result, certain manufacturing costs associated with product shipments of ZULRESSO were expensed prior to FDA approval and, therefore, are not included in cost of goods sold during the years ended December 31, 2022 and 2021.

Research and Development Costs and Accruals

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 U.S. 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 billing terms under these contracts do not coincide with the timing of when the work is performed, the Company is required to make estimates of outstanding obligations to those third parties as of the end of the reporting period. Any accrual estimates are based on a number of factors, including the Company's knowledge of the progress towards completion of the research and development activities, invoicing to date under the contracts, communication from the research institution or other companies of any actual costs incurred during the period that have not yet been invoiced, and the costs included in the contracts. Significant judgments and estimates are 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.

Stock-Based Compensation

The Company recognizes compensation expense for stock-based awards, including grants of stock options and restricted stock units, granted to employees, non-employee directors and non-employee consultants based on the estimated fair value on the date of grant, over the requisite service period. The Company recognizes stock-based compensation expense for only the portion of awards that are expected to vest.

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, using management's best estimates, which consider the inherent risk and uncertainty regarding the future outcomes of the milestones.

The fair value of each stock option grant is estimated using the Black-Scholes option-pricing model. Effective January 1, 2020, the Company began using the historical volatility of only its common stock, as there is adequate historical data for the duration of the expected term.

The expected term of the stock options granted to employees, non-employee directors and non-employee consultants by the Company has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" stock options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the date of grant for time periods approximately equal to the expected term of the award. The expected dividend yield is zero, 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.

Treasury Stock

The Company records treasury stock at cost. Treasury stock consists of shares of the Company's common stock received from a then-employee as consideration for exercises of stock options.

Basic and Diluted Net Income (Loss) Per Share

Basic net income (loss) per share is computed by dividing the net income (loss) by the weighted average number of shares of common stock that were outstanding during the period. For computing diluted net income (loss) per share, the weighted average number of shares of common stock that were outstanding during the period is adjusted for the dilutive effect of common stock equivalents outstanding for the period by using the treasury stock method.

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 anti-dilutive. The Company reported a net loss for the years ended December 31, 2022 and 2021.

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 for its programs. The Company also relies on and expects to continue to rely on third-party manufacturers to supply it with active pharmaceutical ingredients ("API") and formulated drugs; and to provide other services related to manufacturing activities for these programs. These programs could be adversely affected by a significant interruption in the supply of API and formulated drugs, or the interruption of manufacturing related services.

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.

The Company accounts for uncertain tax positions in accordance with the provisions of Accounting Standards Codification ("ASC") Topic 740, "*Income Taxes*" ("Topic 740"). When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. The Company accrues for potential interest and penalties related to unrecognized tax benefits in income tax expense.

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, 2022 and 2021 were carried at fair value, determined according to the fair value hierarchy; see Note 3, Fair Value Measurements.

The carrying amounts reflected in the consolidated balance sheets for the collaboration receivable – related party, accounts payable and accrued expenses approximate their fair values due to their short-term maturities at December 31, 2022 and 2021, 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 to pioneer solutions to deliver life-changing brain health medicines, so every person can thrive.

Comprehensive Income (Loss)

Comprehensive income (loss) includes net income (loss) and other changes in stockholders' equity that result from transactions and economic events other than those with stockholders. The Company's only element of other

comprehensive income (loss) is unrealized gains and losses on marketable securities that are considered to be available-for-sale.

Revenue Recognition

The Company generates revenue from the sale of ZULRESSO, which was approved by the FDA in March 2019 and the Company subsequently began selling in June 2019, and from collaboration and supply agreements with the Company's collaborators. To date, revenue from collaboration agreements has come from initial, upfront payments allocated to licenses of intellectual property delivered to the Company's collaborators and from the supply of material for clinical trials under a supply agreement.

Under ASC Topic 606, *Revenue from Contracts with Customers* ("Topic 606"), an entity recognizes revenue when or as performance obligations are satisfied by transferring control of promised goods or services to a customer, 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(s) 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. 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.

For contracts determined to be within the scope of Topic 606, the Company assesses whether the goods or services promised within each contract are distinct to identify those that are performance obligations. 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 and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract.

The Company allocates the transaction price (the amount of consideration it expects to be entitled to from a customer in exchange for the promised goods or services) to each performance obligation and recognizes the associated revenue when (or as) each performance obligation is satisfied. The Company's estimate of the transaction price for each contract includes all variable consideration to which the Company expects to be entitled.

Collaboration and License Revenue

In assessing whether a promised good or service is distinct in the evaluation of a collaboration or license 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 arrangements with Shionogi and Biogen and concluded that a significant financing component does not exist for either arrangement. For arrangements with licenses of intellectual property that include sales-based royalties or milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties or milestone payments 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 or milestone payment 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. Revenue from the Company's collaboration agreement with Shionogi has come from initial, upfront consideration upon execution of the agreement and for the supply of drug product for Shionogi's clinical trials. Revenue from the Company's collaboration agreement with Biogen has come from initial, upfront consideration related to the execution of the Biogen Collaboration Agreement. For additional information, refer to Note 6, *Collaboration Agreements*.

Product Revenue, Net

The Company recognizes product revenue, net of variable consideration related to certain allowances and accruals that are determined using the expected value method, in its consolidated financial statements at the point in time when control transfers to the customer, which is typically when the product has been delivered to the customer's location. 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. The Company's only performance obligation identified for ZULRESSO is to deliver the product to the location specified by the customer's order. The Company records shipping and handling costs associated with delivery of product to its customers within selling, general and administrative expenses on its consolidated statements of operations and comprehensive income (loss). The Company expenses incremental costs of obtaining a contract as incurred if the expected amortization period of the asset would be less than one year. If the Company were to incur incremental costs with an amortization period greater than a year, such costs would be capitalized as contract assets, as they are expected to be recovered, and would be expensed by amortizing on a systematic basis that is consistent with the transfer to the customer of the goods or services to which the asset relates. The Company did not have any contract assets (unbilled receivables) at December 31, 2022, as customer invoicing generally occurs before or at the time of

revenue recognition. The Company did not have any contract liabilities at December 31, 2022, as the Company did not receive any payments in advance of satisfying its performance obligations to its customers. Amounts billed or invoiced that are considered trade accounts receivable are included in prepaid expenses and other current assets on the consolidated balance sheets.

As of December 31, 2022 and 2021, the Company had not provided any allowance for bad debts against the trade accounts receivable, and the amount of trade accounts receivable was not significant.

The Company records reserves, based on contractual terms, for the following components of variable consideration related to product sold during the reporting period, as well as its estimate of product that remains in the distribution channel inventory of its customers at the end of the reporting period. On a quarterly basis, the Company updates its estimates, if necessary, and records any material adjustments in the period they are identified.

Chargebacks: The Company estimates chargebacks from its customers who directly purchase the product from the Company for discounts resulting from contractual commitments to sell products to eligible healthcare settings at prices lower than the list prices charged to its customers. Customers charge the Company for the difference between what they pay to the Company for the product and the selling price to the eligible healthcare settings. Reserves for chargebacks consist of credits that the Company expects to issue for units that remain in the distribution channel inventories at the end of each reporting period that the Company expects will be sold to eligible healthcare settings, and chargebacks that customers have claimed, but for which the Company has not yet issued a credit.

Government Rebates: The Company is subject to discount obligations under government programs, including Medicaid. The Company records reserves for rebates in the same period the related product revenue is recognized, resulting in a reduction of ZULRESSO product revenue and a current liability that is included in accrued expenses on its consolidated balance sheets. The Company's liability for these rebates consists of invoices received for claims from prior quarters that have not been paid or for which an invoice has not yet been received, estimates of claims for the current quarter, and estimates of future claims that will be made for product that has been recognized as revenue, but which remains in the distribution channel at the end of each reporting period.

Trade Discounts and Allowances: The Company generally provides customary invoice discounts on ZULRESSO sales to its customers for prompt payment and the Company pays fees for sales order management, data, and distribution services. The Company estimates its customers will earn these discounts and fees and deducts these discounts and fees in full from gross ZULRESSO revenue and accounts receivable at the time the Company recognizes the related revenue.

Financial Assistance: The Company provides voluntary financial assistance programs to patients with commercial insurance that have coverage and reside in states that allow financial assistance. The Company estimates the financial assistance amounts for ZULRESSO and records any such amounts within accrued expenses on its consolidated balance sheets. The calculation of the accrual for financial assistance is based on an estimate of claims and the cost per claim that the Company expects to receive using demographics for patients who have registered and been approved for assistance. Any adjustments are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability, which is included as a component of accrued expenses on the consolidated balance sheets.

Product Returns: Consistent with industry practice, the Company offers product return rights to customers for damaged, defective or expiring product, provided it is within a specified period around the product expiration date as set forth in the Company's return goods policy. The Company estimates the amount of its product sales that may be returned by its customers and records this estimate as a reduction of revenue in the period the related product revenue is recognized, as well as a reserve within accrued expenses on the consolidated balance sheets. Product returns have been not significant to date and are not expected to be significant in the future.

Collaborative Arrangements

The Company analyzes its collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and therefore within the scope of ASC Topic 808, *Collaborative Arrangements* ("Topic 808"). This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of Topic 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of Topic 808 and which elements of the collaboration are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606. For elements of collaboration arrangements that are accounted for pursuant to Topic 808, an appropriate recognition method is determined and applied consistently, either by analogy to authoritative accounting literature or by applying a reasonable and rational policy election. For those elements of the arrangement that are accounted for pursuant to Topic 606, the Company applies the five-step model described above, and presents the arrangement as collaboration revenue in the consolidated statements of operations and comprehensive income (loss).

For collaboration arrangements that are within the scope of Topic 808, the Company evaluates the income statement classification for presentation of amounts due from or owed to other participants associated with multiple activities in a collaboration arrangement based on the nature of each separate activity. Payments or reimbursements that are the result of a collaborative relationship instead of a customer relationship, such as co-development and co-commercialization activities, are recorded as research and development expense or selling, general and administrative expense, in the event of a payment to the collaborative partner in a period, or a reduction to these expense line items in the event of a reimbursement from the collaboration partner in a period, as appropriate.

Recently Issued Accounting Pronouncements

In December 2019, the FASB issued ASU No. 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes.* This standard enhances and simplifies various aspects of the income tax accounting guidance in ASC Topic 740, *Income Taxes*, including requirements related to hybrid tax regimes, the tax basis step-up in goodwill obtained in a transaction that is not a business combination, separate financial statements of entities not subject to tax, the intra-period tax allocation exception to the incremental approach, ownership changes in investments, changes from a subsidiary to an equity method investment, interim-period accounting for enacted changes in tax law, and the year-to-date loss limitation in interim-period tax accounting. The Company adopted the standard on the required effective date of January 1, 2021. This guidance did not have a significant impact on the Company's consolidated financial statements and related disclosures.

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 and Level 2 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 in Note 2, Summary of Significant Accounting Policies, marketable 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 Company performs validation procedures to ensure the reasonableness of this data. The Company performs its own review of prices received from the independent pricing services by comparing these

prices to other sources. After completing the validation procedures, the Company did not adjust or override any fair value measurements provided by the pricing services as of December 31, 2022 and 2021.

The following tables summarize the Company's cash equivalents and marketable securities as of December 31, 2022 and 2021:

	December 31, 2022			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(in thousands)			
Cash equivalents:				
Money market funds	$ 161,185	$ 161,185	$ —	$ —
Total cash equivalents	161,185	161,185	—	—
Marketable securities:				
U.S. government securities	302,911	—	302,911	—
U.S. corporate bonds	354,495	—	354,495	—
International corporate bonds	127,248	—	127,248	—
U.S. commercial paper	63,114	—	63,114	—
International commercial paper	133,163	—	133,163	—
U.S. certificates of deposit	15,613	—	15,613	—
U.S. municipal securities	113,250	—	113,250	—
Total marketable securities	1,109,794	—	1,109,794	—
	$1,270,979	$ 161,185	$1,109,794	$ —

	December 31, 2021			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(in thousands)			
Cash equivalents:				
Money market funds	$ 289,440	$ 289,440	$ —	$ —
U.S. commercial paper	2,000	—	2,000	—
International commercial paper	1,999	—	1,999	—
Total cash equivalents	293,439	289,440	3,999	—
Marketable securities:				
U.S. government securities	324,532	—	324,532	—
U.S. corporate bonds	627,780	—	627,780	—
International corporate bonds	236,812	—	236,812	—
U.S. commercial paper	80,176	—	80,176	—
International commercial paper	142,335	—	142,335	—
U.S. municipal securities	36,428	—	36,428	—
Total marketable securities	1,448,063	—	1,448,063	—
	$ 1,741,502	$ 289,440	$ 1,452,062	$ —

During the years ended December 31, 2022 and 2021, there were no transfers among the Level 1, Level 2 and Level 3 categories.

The following tables summarize the gross unrealized gains and losses of the Company's marketable securities as of December 31, 2022 and 2021:

	December 31, 2022				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
			(in thousands)		
Assets:					
U.S. government securities	$ 307,173	$ —	$ (4,262)	$ —	$ 302,911
U.S. corporate bonds	358,019	6	(3,530)	—	354,495
International corporate bonds	128,374	7	(1,133)	—	127,248
U.S. commercial paper	63,234	—	(120)	—	63,114
International commercial paper	133,338	—	(175)	—	133,163
U.S. certificates of deposit	15,613	—	—	—	15,613
U.S. municipal securities	114,249	31	(1,030)	—	113,250
	$ 1,120,000	$ 44	$ (10,250)	$ —	$ 1,109,794

	December 31, 2021				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
			(in thousands)		
Assets:					
U.S. government securities	$ 325,514	$ —	$ (982)	$ —	$ 324,532
U.S. corporate bonds	628,836	27	(1,083)	—	627,780
International corporate bonds	237,303	—	(491)	—	236,812
U.S. commercial paper	80,194	—	(18)	—	80,176
International commercial paper	142,358	—	(23)	—	142,335
U.S. municipal securities	36,518	—	(90)	—	36,428
	$ 1,450,723	$ 27	$ (2,687)	$ —	$ 1,448,063

The following tables summarize the fair value and the unrealized losses of the Company's marketable securities that have been in a loss position for either less than twelve months or greater than twelve months as of December 31, 2022 and 2021:

	December 31, 2022					
	Less than 12 months		Greater than 12 months		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
			(in thousands)			
U.S. government securities	$ 112,243	$ (1,517)	$ 185,691	$ (2,745)	297,934	$ (4,262)
U.S. corporate bonds	208,507	(1,989)	130,633	(1,541)	339,140	(3,530)
International corporate bonds	50,982	(497)	68,993	(636)	119,975	(1,133)
U.S. commercial paper	24,768	(120)	—	—	24,768	(120)
International commercial paper	30,987	(175)	—	—	30,987	(175)
U.S. municipal securities	86,251	(497)	14,466	(533)	100,717	(1,030)
	$ 513,738	$ (4,795)	$ 399,783	$ (5,455)	$ 913,521	$ (10,250)

	December 31, 2021					
	Less than 12 months		Greater than 12 months		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
	(in thousands)					
U.S. government securities	$ 309,588	$ (982)	$ —	$ —	$ 309,588	$ (982)
U.S. corporate bonds	601,475	(1,083)	—	—	601,475	(1,083)
International corporate bonds	231,672	(491)	—	—	231,672	(491)
U.S. commercial paper	21,968	(18)	—	—	21,968	(18)
International commercial paper	35,059	(23)	—	—	35,059	(23)
U.S. municipal securities	24,953	(90)	—	—	24,953	(90)
	$ 1,224,715	$ (2,687)	$ —	$ —	$ 1,224,715	$ (2,687)

As of December 31, 2022 and 2021, the unrealized losses on the Company's investments in U.S. government securities, U.S. corporate bonds, and international corporate bonds were caused by interest rate increases. The Company purchased those investments at a premium relative to their face amount. The current credit ratings are all within the guidelines of the investment policy of the Company and the Company does not expect the issuers to settle any security at a price less than the amortized cost basis of the investment. The Company does not intend to sell the investments and it is not probable that the Company will be required to sell the investments before recovery of their amortized cost basis.

As of December 31, 2022, all marketable securities held by the Company had remaining contractual maturities of one year or less, except for U.S. government securities, U.S. corporate bonds, international corporate bonds and municipal securities with a fair value of $211.2 million that had maturities of one to two years.

As of December 31, 2021, all marketable securities held by the Company had remaining contractual maturities of one year or less, except for U.S. government securities, U.S. corporate bonds, international corporate bonds and municipal securities with a fair value of $436.1 million that had maturities of one to two years.

All marketable securities, including those with remaining contractual maturities of more than one year, are classified as current assets on the balance sheet because they are considered to be "available for sale" and the Company can convert them into cash to fund current operations.

There have been no impairments of the Company's assets measured and carried at fair value during the years ended December 31, 2022 and 2021.

4. Balance Sheet Components

Property and Equipment, net

The following table summarizes property and equipment, net, as of December 31, 2022 and 2021:

	December 31, 2022	December 31, 2021
	(in thousands)	
Computer hardware and software	$ 1,771	$ 1,391
Furniture and equipment	1,714	1,208
Leasehold improvements	5,508	5,390
	8,993	7,989
Less: Accumulated depreciation	(6,095)	(4,973)
	$ 2,898	$ 3,016

Depreciation expense for the years ended December 31, 2022, 2021 and 2020 was $1.1 million, $4.2 million and $2.6 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

The following tables summarizes accrued expenses as of December 31, 2022 and 2021:

	December 31, 2022	December 31, 2021
	(in thousands)	
Accrued research and development costs	$ 32,565	$ 39,147
Employee-related	29,372	18,618
Professional services	10,172	8,893
Other	557	617
	$ 72,666	$ 67,275

5. Leases, Commitments and Contingencies

Operating Leases

The Company leases office space and certain equipment. All of the leases recorded on the consolidated balance sheets are operating leases. The Company's leases have remaining lease terms ranging from less than one year to approximately two years. Some of the leases include options to extend the leases for up to five years. These options were not included for the purpose of determining the right-of-use assets and associated lease liabilities as the Company determined that the renewal of these leases is not reasonably certain so only the original lease term was taken into consideration. The leases do not include any restrictions or covenants that had to be accounted for under the lease guidance.

As of January 1, 2020, the Company leased office space in three multi-tenant buildings in Cambridge, Massachusetts, consisting of 63,017 square feet in the first building, under an operating lease that will expire on August 31, 2024; 40,419 square feet in the second building, under an operating lease that will expire on August 31, 2024 and 15,975 square feet in the third building, under an operating lease that began on March 1, 2019 and was initially scheduled to expire on February 29, 2024; and in a multi-tenant building in Raleigh, North Carolina, consisting of 15,525 square feet under an operating lease that will expire on November 30, 2024.

During the year ended December 31, 2021, the Company terminated the operating lease for office space in the third multi-tenant building in Cambridge, Massachusetts and the remaining right-of-use asset of $3.7 million and the associated liabilities related to this lease were de-recognized upon termination of the lease. Additionally, during the year ended December 31, 2021, the Company entered into a sublease for a portion of the leased office space in the second multi-tenant building in Cambridge, Massachusetts.

From June 2018 to January 2019, the Company entered into leases for vehicles for field-based employees. These leases were determined to be operating leases and a right-of-use operating asset in the amount of $5.3 million was recorded on the balance sheet upon implementation of the new lease standard on January 1, 2019. The leases were for a term of three years and were to expire on various dates through January 31, 2022. During the year ended December 31, 2020, these leases were terminated as part of the restructuring during April 2020, and the remaining right-of-use asset of $2.3 million and the associated liabilities related to these leases were de-recognized upon termination of the leases. During the year ended December 31, 2020, the restricted cash of $0.7 million related to these leases was returned to the Company by the lessor.

The following table shows the amounts of operating leases in the balance sheets as of December 31, 2022 and 2021:

Balance sheet location	Balance sheet caption	December 31, 2022	December 31, 2021
		(in thousands)	
Assets			
Right-of-use operating asset	Right-of-use operating asset	$ 10,532	$ 16,109
Liabilities			
Current operating lease liabilities	Operating lease liability, current portion	7,643	7,468
Long-term operating lease liabilities	Operating lease liability, net of current portion	4,491	10,964
		$ 12,134	$ 18,432

The following table shows the amounts of lease expense by lease type that was recognized during the years ended December 31, 2022, 2021 and 2020:

	Year Ended December 31, 2022	2021	2020
		(in thousands)	
Operating lease cost	$ 6,748	$ 8,748	$ 8,838
Variable lease cost	1,846	1,600	2,285
Short-term lease cost	206	101	74
Sublease income	(421)	(234)	-
	$ 8,379	$ 10,215	$ 11,197

The Company made an accounting policy election not to apply the recognition requirements to short-term leases. The Company recognizes the lease payments for short-term leases as expense on a straight-line basis over the lease term, and variable lease payments in the period in which the obligation for those payments is incurred.

The minimum lease payments are expected to be as follows:

Years Ending December 31,	(In thousands)
2023	$ 7,643
2024	5,316
Thereafter	-
Total lease payments	12,959
Less imputed interest	(825)
Present value of operating lease liabilities	$ 12,134

The following table shows the weighted average remaining lease term and weighted average discount rate of the operating leases:

	Year ended December 31,	
	2022	2021
Weighted average remaining lease term in years	1.68	2.68
Weighted average discount rate	7.5%	7.5%

The interest rate implicit in lease contracts is typically not readily determinable and as such, the Company uses its incremental borrowing rate based on the information available at the lease commencement date, which represents an internally developed rate that would be incurred to borrow, on a collateralized basis, over a similar term, an amount equal to the lease payments in a similar economic environment.

The following table shows the supplemental disclosure of cash flow information related to the operating leases included in cash flows used by operating activities in the consolidated statements of cash flows:

	Year Ended December 31,		
	2022	2021	2020
		(in thousands)	
Cash paid for amounts included in the measurement of lease liabilities	$ 7,468	$ 9,264	$ 9,231
Lease asset de-recognized upon lease cancellation			
Operating leases	$ —	$ 3,733	$ 2,310

License Agreements

CyDex License Agreement

In September 2015, the Company amended and restated its existing commercial license agreement with CyDex Pharmaceuticals, Inc. (“CyDex”), a wholly owned subsidiary of Ligand Pharmaceuticals Incorporated.

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 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. The Company is required to pay a royalty to CyDex on sales of brexanolone and will be required to pay a royalty on any sales of SAGE-689, if such product candidate is successfully developed in the future. Royalty rates are in the low single digits based on levels of net sales. From the effective date of the agreement to December 31, 2022, the Company has paid to CyDex $1.0 million for licensing fees, which was recorded as research and development expense.

Under the amended and restated license agreement with CyDex, the Company agreed to make milestone payments 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. From the effective date of the agreement to December 31, 2022, the Company has recorded research and development expense and made cash payments of $3.6 million related to these clinical development and regulatory milestones and has recorded an intangible asset and made a cash payment of $3.0 million related to these regulatory milestones.

For the year ended December 31, 2020, 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 accrued expenses totaling $1.3 million. The amount was paid in cash during the year ended December 31, 2021.

For the year ended December 31, 2021, an additional clinical development milestone was met under the license agreement with CyDex related to SAGE-689, and accordingly, the Company recorded research and development expense and made a cash payment of $0.1 million. Additionally in the year ended December 31, 2021, the Company paid $1.3 million for the additional clinical development milestones that were met for the brexanolone program under the license agreement with CyDex in the year ended December 31, 2020.

For the year ended December 31, 2022, the Company did not record any expense or intangible asset, or make any milestone payments related to clinical development or regulatory milestones for the brexanolone program or SAGE-689 under the license agreement with CyDex.

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 ("the Regents") 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. The Company paid to the Regents clinical development milestones of $0.1 million, prior to December 31, 2015; no other milestones are outstanding under this non-exclusive license agreement. The Company is 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, and the Company began to pay these royalties in 2019. 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 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 was required to make payments of $15,000 for annual maintenance fees until the calendar year following the first sale of ZULRESSO. 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. The Company pays royalties at a low single digit percentage of net sales of ZULRESSO, 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. From the effective date of the agreement to December 31, 2022, the Company has recorded research and development expense and made cash payments of $0.3 million related to these regulatory and sales milestones; and has recorded an intangible asset and made a cash payment of $0.5 million related to these regulatory and sales milestones.

For the years ended December 31, 2022, 2021 and 2020, the Company did not record any expense or make any milestone payments under the license agreements with the Regents.

6. Collaboration Agreements

Shionogi

In June 2018, the Company entered into a strategic collaboration with Shionogi for the clinical development and commercialization of zuranolone for the treatment of MDD and other potential indications in Japan, Taiwan and South Korea (the “Shionogi Territory”). In October 2018, the Company entered into a supply agreement with Shionogi for the Company to supply zuranolone clinical material to Shionogi.

Under the terms of the collaboration agreement, Shionogi is responsible for all clinical development and regulatory filings for zuranolone in MDD and other indications in the Shionogi Territory and would be responsible for commercialization of zuranolone in the Shionogi Territory, if zuranolone is successfully developed and obtains marketing approval in any of the countries within the Shionogi Territory. 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. The Company is eligible to receive tiered royalties on sales of zuranolone in the Shionogi Territory, 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 zuranolone in Japan. As between the Company and Shionogi, the Company maintains exclusive rights to develop and commercialize zuranolone outside of the Shionogi Territory. The upfront cash payment and any payments for milestones and royalties are non-refundable and non-creditable. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any milestone payments or any royalty payments from Shionogi.

The Company concluded that Shionogi meets the definition of a customer because the Company is delivering intellectual property and know-how rights for the zuranolone 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 to which the Company was entitled in exchange for the goods or services that will be delivered to Shionogi.

The Company determined that the performance obligations in the Shionogi collaboration agreement included the license to zuranolone and the supply of certain materials during the clinical development phase, which includes the supply of API. The performance obligation related to the license to zuranolone was determined to be distinct from other performance obligations and therefore was a separate performance obligation for which control was transferred upon signing. The obligation to provide certain clinical materials, including API for use during the development period, was determined to be a separate performance obligation. Given that Shionogi is not obligated to purchase any minimum amount or quantities of commercial API, the supply of API to Shionogi for commercial use was determined to be an option for Shionogi, rather than a performance obligation of the Company at contract inception and will be accounted for if and when exercised. The Company also determined that there was no separate material right in connection with the supply of API for commercial use as the expected pricing was not at a discount. Given this fact pattern, the Company has concluded the agreement has two performance obligations.

Under the clinical supply agreement, the Company is obligated to manufacture and supply to Shionogi (i) clinical quantities of API reasonably required by Shionogi for the development of licensed products in the Shionogi territory and (ii) quantities of drug product reasonably required for use by Shionogi in Phase 1 clinical trials of zuranolone in the Shionogi territory, in the quantities agreed to by the parties. Collaboration revenue from the clinical supply agreement pertains to the clinical material sold under the terms of the clinical supply agreement. The Company records the costs related to the clinical supply agreement in research and development expense on its consolidated statements of operations and comprehensive income (loss). During the years ended December 31, 2022, 2021 and 2020, no collaboration revenue was recognized related to the Company's agreement with Shionogi.

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 upon delivery of the license to Shionogi and resulting ability of Shionogi to use and benefit from the license, which was in the three months ended June 30, 2018. 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 re-evaluate 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.

Biogen

In November 2020, the Company entered into the Biogen Collaboration Agreement to jointly develop and commercialize SAGE-217 products for MDD, PPD and other disorders and SAGE-324 products for essential tremor and other disorders. Concurrently, the Company also entered into a stock purchase agreement with BIMA (the "Biogen Stock Purchase Agreement") under which BIMA purchased shares of the Company's common stock. The Biogen Collaboration Agreement became effective on December 28, 2020 (the "Effective Date").

Under the terms of the Biogen Collaboration Agreement, the Company granted Biogen co-exclusive licenses to develop and commercialize SAGE-217 products and SAGE-324 products (each, a "Product Class" and together, the "Licensed Products") in the U.S., an exclusive license to develop and commercialize SAGE-217 products in all countries of the world other than the U.S. and the Shionogi Territory, and an exclusive license to develop and commercialize SAGE-324 products in all countries of the world other than the U.S. The Company refers to the territories outside the U.S. to which Biogen has rights under the Biogen Collaboration Agreement with respect to the applicable Licensed Product as the "Biogen Territory".

In connection with the effectiveness of the Biogen Collaboration Agreement and the closing of the sale of shares to BIMA in December 2020, the Company received $1.5 billion in consideration, comprised of an upfront payment of $875.0 million and the $650.0 million purchase price for 6,241,473 newly issued shares of the Company's common stock (the "Biogen Shares"). As a result of the purchase of the Biogen Shares, Biogen has become a related party of the Company.

The Company is eligible to receive additional payments of up to $1.6 billion if certain regulatory and commercial milestones are achieved. The potential future milestone payments for SAGE-217 products include up to $475.0 million for the achievement of specified regulatory and commercial milestones, including milestones totaling $225.0 million for the first commercial sale of zuranolone in MDD and PPD, and up to $300.0 million for the achievement of specified net sales milestones. The potential future milestone payments for SAGE-324 products include up to $520.0 million for the achievement of specified regulatory and commercial milestones and up to $300.0 million for the achievement of specified net sales milestones. The Company is also eligible to receive tiered royalties on net sales of SAGE-217 products and SAGE-324 products in the Biogen Territory at percentage rates ranging from the high teens to low twenties.

Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may never receive any milestone payments or any royalty payments under the Biogen Collaboration Agreement.

Development and commercialization activities in the U.S. are conducted pursuant to plans agreed to by the Company and Biogen and overseen by a joint steering committee that will consist at all times of an equal number of representatives of each party. The Company and Biogen will share equally in the costs for development and commercialization, as well as the profits and losses upon FDA approval and commencement of product sales, in the U.S., subject to the Company's opt-out right described below. Biogen will be solely responsible for all development activities and costs related to any development and commercialization of SAGE-217 products and SAGE-324 products for the Biogen Territory, and the Company will receive royalties on any sales in the Biogen Territory, as mentioned above. Biogen will be the principal and record sales of SAGE-217 products globally. The Company will be the principal and record sales of SAGE-324 products in the U.S. and Biogen will record sales of SAGE-324 Products in the Biogen Territory.

The Company will supply API and bulk drug product for the Biogen Territory and API, bulk drug product and final drug product for the U.S. to support development and commercialization activities. Biogen has the right to assume manufacturing responsibilities for API for the Biogen Territory at any time during the term of the agreement and will, within a reasonable period of time after the Effective Date, assume manufacturing responsibility for bulk drug product for the Biogen Territory.

Unless terminated earlier, the Biogen Collaboration Agreement will continue on a Licensed Product-by-Licensed Product and country-by-country basis until the date on which (a) in any country in the Biogen Territory, the royalty term has expired for all Licensed Products in a Product Class in such country, and (b) for the U.S., the parties agree to permanently cease to commercialize all Licensed Products in a Product Class. Biogen also has the right to terminate the Biogen Collaboration Agreement for convenience in its entirety, on a Product Class-by-Product Class basis or as to a particular region, upon advance written notice. The Company has an opt-out right to convert the co-exclusive licenses in the U.S. to an exclusive license to Biogen on a Product Class-by-Product Class basis. Following the exercise of the opt-out right, the Company would no longer share equally in the profits and losses in the U.S. and would be entitled to receive certain royalty payments at percentage rates ranging from the high teens to low twenties and additional sales milestones.

The Company concluded that the Biogen Collaboration Agreement and the Biogen Stock Purchase Agreement should be combined and treated as a single arrangement for accounting purposes as the agreements were entered into contemporaneously and in contemplation of one another. The Company determined that the combined agreements had elements that were within the scope of Topic 606 and Topic 808.

As of the Effective Date, the Company identified the following promises in the Biogen Collaboration Agreement that were evaluated under the scope of Topic 606: delivery of (i) a co-exclusive license for SAGE-217 products in the U.S.; (ii) an exclusive license for SAGE-217 products in the Biogen Territory; (iii) a co-exclusive license for SAGE-324 products in the U.S.; (iv) an exclusive license for SAGE-324 products in the Biogen Territory; (v) the clinical manufacturing supply of API and bulk drug product for SAGE-217 products in the Biogen Territory; and (vi) the clinical manufacturing supply of API and bulk drug product for SAGE-324 products in the Biogen Territory.

The Company also evaluated whether certain options outlined within the Biogen Collaboration Agreement represented material rights that would give rise to a performance obligation and concluded that none of the options convey a material right to Biogen and therefore are not considered separate performance obligations within the Biogen Collaboration Agreement.

The Company assessed the above promises and determined that the co-exclusive licenses for SAGE-217 products and SAGE-324 products in the U.S. are reflective of a vendor-customer relationship and therefore represent performance obligations within the scope of Topic 606. The co-exclusive license for SAGE-217 products and SAGE-324 products in the U.S. are considered functional intellectual property and distinct from other promises under the contract. The exclusive licenses for SAGE-217 products and SAGE-324 products in the Biogen Territory are considered functional licenses that are distinct in the context of the Biogen Collaboration Agreement as Biogen can benefit from the licenses on its own or together with other readily available resources. As the co-exclusive licenses in the U.S. and the exclusive licenses in the Biogen Territory are delivered at the same time, they are considered one performance obligation at contract inception. The clinical manufacturing supply of API and bulk drug product for SAGE-217 products and SAGE-324 products for the Biogen Territory are considered distinct in the context of the Biogen Collaboration Agreement as Biogen can benefit from the manufacturing services together with the licenses transferred by the Company at the inception of the agreement. Therefore, each represents a separate performance obligation within a contract with a customer under the scope of Topic 606 at contract inception.

The Company considers the collaborative activities associated with the co-development, co-commercialization, and co-manufacturing of SAGE-217 products and SAGE-324 products in the U.S. to be separate units of account within the scope of Topic 808 as the Company and Biogen are both active participants in the development and commercialization activities and are exposed to significant risks and rewards that are dependent on the development and commercial success of the activities in the arrangement. The Company has determined that the supply of API and bulk drug product for the Biogen Territory and API, bulk drug product and final drug product for the U.S. to Biogen will be classified as collaboration revenue – related party in the consolidated statements of operations and comprehensive income (loss). During the years ended December 31, 2022 and 2021, no collaboration revenue – related party was recognized related to the Biogen Collaboration Agreement.

Payments to or reimbursements from Biogen related to the co-development, co-commercialization, and co-manufacturing activities and the agreement of the parties to share equally the cost of these activities will be accounted for

as an increase to or reduction of research and development expenses or selling, general and administrative expenses, depending on the nature of the activity.

During the year ended December 31, 2022, the Company recorded a net reimbursement of $75.5 million for the amounts due from Biogen as a reduction of the related operating expense categories in the consolidated statement of operations and comprehensive income (loss). During the year ended December 31, 2021, the Company recorded a net reimbursement of $91.1 million for the amounts due from Biogen as a reduction of the related operating expense categories in the consolidated statement of operations and comprehensive income (loss).

As of December 31, 2022, the Company recorded a Collaboration Receivable – Related Party of $13.7 million in the consolidated balance sheet for the amounts due for the three months ended December 31, 2022. During the year ended December 31, 2022, no payments were made to Biogen and the Company received $80.3 million from Biogen for the amounts due for the three months ended December 31, 2021 and the nine months ended September 30, 2022.

The following table summarizes expenses related to the Biogen Collaboration Agreement that were incurred by the Company and the related reimbursement from Biogen, reflected by category of operating expenses:

	Year Ended December 31,	
	2022	2021
	(in thousands)	
Expenses related to the Biogen Collaboration Agreement incurred by Sage	$ 213,524	$ 193,776
Net reimbursement from Biogen reflected in the consolidated statements of operations and comprehensive income (loss):		
Research and development expenses	(73,227)	(79,848)
Selling, general and administrative expenses	(2,230)	(11,282)
	(75,457)	(91,130)
Total net expenses related to the Biogen Collaboration Agreement in the consolidated statements of operations and comprehensive income (loss)	$ 138,067	$ 102,646

The Company determined the transaction price under Topic 606 at the inception of the Biogen Collaboration Agreement to be $1.1 billion, consisting of the upfront payment of $875.0 million plus $232.5 million in excess proceeds from the equity investment under the Biogen Stock Purchase Agreement, when measured at fair value, plus future variable consideration for manufacturing supply of clinical API and bulk drug product for the Biogen Territory. The amount of variable consideration related to the future manufacturing services was not material. The Company determined that any variable consideration related to clinical development and regulatory milestones is deemed to be fully constrained and therefore excluded from the transaction price due to the high degree of uncertainty and risk associated with these potential payments, as the Company determined that it could not assert that it was probable that a significant reversal in the amount of cumulative revenue recognized will not occur. The Company also determined that royalties and sales milestones relate solely to the licenses of intellectual property and are therefore excluded from the transaction price under the sales- or usage-based royalty exception of Topic 606. Revenue related to these royalties and sales milestones will only be recognized when the associated sales occur, and relevant thresholds are met.

As noted above, the Company identified three performance obligations in the Biogen Collaboration Agreement: (i) the delivery of the co-exclusive licenses for SAGE-217 products and SAGE-324 products in the U.S. and the exclusive licenses for SAGE-217 products and SAGE-324 products in the Biogen Territory; (ii) the clinical manufacturing supply of API and bulk drug product for SAGE-217 products in the Biogen Territory; and (iii) the clinical manufacturing supply of the API and bulk drug product for SAGE-324 products in the Biogen Territory. The selling price of each performance obligation in the Biogen Collaboration Agreement was determined based on the Company's SSP with the objective of determining the price at which it would sell such an item if it were to be sold regularly on a standalone basis. The Company allocated the variable consideration related to the manufacturing obligations to the future clinical supply of SAGE-217 products and SAGE 324 products in the Biogen Territory and the remaining fixed consideration to the license

obligation. The variable consideration related to the manufacturing obligations was not material. As such, the entirety of the $1.1 billion fixed consideration of the transaction price has been allocated to the transfer of the co-exclusive licenses for SAGE-217 products and SAGE-324 products in the U.S. and the exclusive licenses for SAGE-217 products and SAGE-324 products in the Biogen Territory. The Company recognizes revenue for the license performance obligations at a point in time, that is upon transfer of the licenses to Biogen. As control of these licenses was transferred on the Effective Date and Biogen could begin to use and benefit from the licenses, the Company recognized $1.1 billion of license revenue during the year ended December 31, 2020 under the Biogen Collaboration Agreement. The Company will recognize revenue for the clinical manufacturing supply obligations at a point in time, that is upon the delivery of the supply to Biogen.

Accounting for the Biogen Stock Purchase Agreement

In connection with the execution of the Biogen Collaboration Agreement, the Company and BIMA entered into the Biogen Stock Purchase Agreement. Pursuant to the Biogen Stock Purchase Agreement, the Company sold the Biogen Shares to BIMA at a price of approximately $104.14 per share, which represented a 40 percent premium over the 30-day volume-weighted average share price as of the last trading day prior to the date the Biogen Collaboration Agreement and Biogen Stock Purchase Agreement were executed in November 2020, for aggregate consideration of $650.0 million. The sale of the shares to BIMA closed on December 31, 2020.

The Biogen Stock Purchase Agreement includes certain standstill provisions, lock-up restrictions, and a voting agreement with respect to the Biogen Shares. Pursuant to the terms of the Biogen Stock Purchase Agreement, BIMA has agreed not to, and to cause its affiliates not to, directly or indirectly acquire the Company's securities, seek or propose a tender or exchange offer or merger between the Company and Biogen, solicit proxies or consents with respect to any matter, or undertake other specified actions, in each case subject to specified conditions. The standstill restrictions terminate on the earliest of (i) a specified regulatory milestone under the Biogen Collaboration Agreement, (ii) the date one year following the termination of the Biogen Collaboration Agreement and (iii) the seventh anniversary of the Effective Date. BIMA also agreed not to, and to cause its affiliates not to, sell or transfer any of the Biogen Shares for a period of eighteen months from the closing of the sale of the Biogen Shares, which period expired on June 30, 2022, and to limit sales and transfers of the Biogen Shares for an additional eighteen-month period, in each case subject to specified conditions and exceptions.

The Company determined the fair value of the common shares issued using an option pricing valuation model to take into consideration the holding period restrictions. The fair value of the Company's common stock was considered a Level 2 fair value measurement within the fair value hierarchy. The most significant assumptions within the model are the Company's stock price, the term of the restrictions and the stock price volatility, which is based upon a blend of historical and implied volatility of the Company's stock. Based on the fair value adjustments made by management, the fair value of the shares issued was determined to be $417.5 million, which was $232.5 million less than the proceeds received from BIMA for the issuance of the Company's common stock under the Biogen Stock Purchase Agreement. As such, the $232.5 million in excess proceeds has been included in the $1.1 billion transaction price of the Biogen Collaboration Agreement determined above.

7. Preferred Stock

The Board of Directors of the Company (the "Board") 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 can designate the rights, preferences and privileges of the shares of each series and any of its qualifications, limitations or restrictions. The Board 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, 2022 and 2021, 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, 2022 and 2021, 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, if any. As of December 31, 2022 and 2021, no dividends have been declared.

On December 31, 2020, the Company completed the sale of 6,241,473 shares of its common stock in a private placement to BIMA at a price of approximately $104.14 per share, resulting in aggregate gross proceeds to the Company of $650.0 million. For additional information, refer to Note 6, *Collaboration Agreements*.

As of December 31, 2022, the Company had received 3,033 shares of the Company's common stock from a then-employee as consideration for exercises of stock options. The total cost of shares held in treasury at December 31, 2022 was $0.4 million.

9. Stock-Based Compensation

Equity Plans

On July 2, 2014, the stockholders of the Company approved the 2014 Stock Option and Incentive Plan (the "2014 Plan"), which became effective immediately prior to the completion of the Company's IPO. The 2014 Plan provides for the grant of restricted stock awards, restricted stock units, incentive stock options and non-statutory stock options. The 2014 Plan replaced the Company's 2011 Stock Option and Grant Plan (the "2011 Plan"). The Company no longer grants stock options or other awards under its 2011 Plan, but any stock options outstanding under the 2011 Plan remain outstanding and effective in accordance with their terms.

The 2014 Plan provides for an annual increase, to be added on the first day of each fiscal year, by up to 4% of the Company's outstanding shares of common stock as of the last day of the prior year. On January 1, 2022, 2,357,482 shares of common stock, representing 4% of the Company's outstanding shares of common stock as of December 31, 2021, were added to the 2014 Plan.

On December 15, 2016, the Board approved the 2016 Inducement Equity Plan (as amended and restated, the "2016 Plan"). The 2016 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 Plan to increase the total number of shares reserved for issuance by 1,200,000 shares.

Terms of equity grants, including vesting requirements, are determined by the Board or the Compensation Committee of the Board, subject to the provisions of the applicable plan. Stock options granted by the Company that are not performance-based are considered time-based because they 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% vesting at the one-year anniversary. All stock option awards expire 10 years after the date of grant.

As of December 31, 2022, the total number of shares underlying outstanding awards under all equity plans was 9,203,831 and the total number of shares available for future issuance under all equity plans was 7,086,615 shares.

Restricted Stock Units

The following table summarizes activity relating to time-based restricted stock units and performance restricted stock units:

	Shares	Weighted Average Grant Date Fair Value
Outstanding as of December 31, 2021	1,256,098	$ 57.87
Granted	705,380	40.02
Vested	(366,014)	40.13
Forfeited	(179,983)	95.84
Outstanding as of December 31, 2022	1,415,481	48.73

Time-based restricted stock units

During the year ended December 31, 2020, the Company granted 550,890 time-based restricted stock units to certain employees of the Company. These time-based restricted stock units vested over two years, with 25% vesting at the one-year anniversary of the grant date and 75% vesting at the two-year anniversary of the grant date, which was in April 2021 and April 2022, respectively. During the year ended December 31, 2021, 113,941 of these time-based restricted stock units vested, with a fair value on the date of vesting equal to $8.8 million. During the year ended December 31, 2022, 291,505 of these time-based restricted stock units vested, with a fair value on the date of vesting equal to $9.5 million. During the year ended December 31, 2020, no time-based restricted stock units vested.

During the year ended December 31, 2021, the Company granted 268,119 time-based restricted stock units to certain employees of the Company. These time-based restricted stock units vest over four years, with 25% vesting at the one-year anniversary of the vesting start date, which was in September 2022; and the remaining 75% will vest ratably in quarterly increments over the remaining three years. During the year ended December 31, 2022, 74,509 of these time-based restricted stock units vested, with a fair value on the date of vesting equal to $2.9 million.

During the year ended December 31, 2022, the Company granted no time-based restricted stock units.

At December 31, 2022, 160,403 time-based restricted stock units were both outstanding and unvested, and the total unrecognized stock-based compensation expense related to these awards was $5.0 million.

Performance restricted stock units

During the year ended December 31, 2020, the Company granted 471,386 performance restricted stock units to employees of the Company. These performance restricted stock units are related to the achievement of certain clinical and regulatory development milestones related to product candidates and commercial milestones.

During the year ended December 31, 2021, the Company granted 531,176 performance restricted stock units to employees of the Company. These performance restricted stock units are related to the achievement of certain clinical and regulatory development milestones related to product candidates and commercial milestones.

During the year ended December 31, 2022, the Company granted 705,380 performance restricted stock units to its employees and consultants. These performance restricted stock units are 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 performance restricted stock units 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 milestones.

As of December 31, 2022, 2021 and 2020, for performance restricted stock units that were outstanding, the achievement of the milestones that had not been met was considered not probable, and therefore no expense has been recognized related to these awards in the years ended December 31, 2022, 2021 and 2020, respectively.

No performance restricted stock units vested during the years ended December 31, 2022 and 2020.

During the year ended December 31, 2021, two milestones for outstanding performance restricted stock units were achieved. For the first milestone that was met, the fair value of the performance restricted stock units that vested upon achievement was $6.1 million and the Company recognized stock-based compensation expense related to this milestone of $3.8 million. 39% of the performance restricted stock units that were granted during the year ended December 31, 2020 included this milestone as a vesting condition. For the second milestone that was met, the fair value of the performance restricted stock units that vested upon achievement was $3.4 million and the Company recognized stock-based compensation expense related to this milestone of $12.8 million. 38% of the performance restricted stock units that were granted during the year ended December 31, 2019 included this milestone as a vesting condition.

At December 31, 2022, 1,255,078 performance restricted stock units were both outstanding and unvested, and the total unrecognized stock-based compensation expense related to these awards was $62.4 million.

Stock Option Rollforward

The following table summarizes activity related to time-based and performance-based stock options:

	Shares	Weighted Average Exercise Price	Weighted Average Remaining Life (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2021	7,283,439	$ 84.17	6.74	$ 16,590
Granted	1,181,487	$ 39.45		
Exercised	(156,195)	$ 7.84		
Forfeited	(520,381)	$ 98.65		
Outstanding as of December 31, 2022	7,788,350	$ 77.95	6.36	$ 7,275
Vested and expected to vest as of December 31, 2022	6,724,505	$ 78.86	6.05	$ 6,917
Exercisable as of December 31, 2022	5,109,027	$ 85.76	5.22	$ 5,607

As of December 31, 2022, the Company had unrecognized stock-based compensation expense related to its outstanding and unvested time-based stock option awards of $61.0 million, which is expected to be recognized over the remaining weighted average vesting period of 2.94 years.

The intrinsic value of stock options exercised during the years ended December 31, 2022, 2021 and 2020 was $4.4 million, $9.0 million and $2.1 million, respectively.

Performance-Based Stock Options

Recognition of stock-based compensation expense associated with 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 milestones.

As of December 31, 2022, 2021 and 2020, for performance-based stock option grants that were outstanding, the achievement of the milestones that had not been met was considered not probable, and therefore no expense has been recognized related to these awards in the years ended December 31, 2022, 2021 and 2020, respectively.

During the year ended December 31, 2021, in connection with the hiring of its chief executive officer, the Company granted 650,000 stock options to its chief executive officer to purchase shares of common stock that contain performance-based vesting criteria, such that the shares underlying such stock options will vest upon the achievement of certain regulatory and commercial milestones. During the years ended December 31, 2022 and 2020, the Company granted no stock options to purchase shares of common stock that contain performance-based vesting criteria.

During the years ended December 31, 2022, 2021 and 2020, no milestones were achieved under performance-based stock options.

As of December 31, 2022, 650,000 performance-based stock options were both outstanding and unvested, the total unrecognized stock-based compensation expense related to these awards was $8.2 million and the timing of recognition of this stock-based compensation expense is subject to judgment of the Company as to when the performance conditions are considered probable of being achieved.

Stock-Based Compensation Expense

The following table summarizes stock-based compensation expense recognized during the years ended December 31, 2022, 2021 and 2020:

	Year Ended December 31,		
	2022	2021	2020
		(in thousands)	
Research and development	$ 25,888	$ 49,746	$ 42,370
Selling, general and administrative	35,714	54,883	51,836
Restructuring	—	—	1,788
	$ 61,602	$ 104,629	$ 95,994

The following table summarizes stock-based compensation expense by award type recognized during the years ended December 31, 2022, 2021 and 2020:

	Year Ended December 31,		
	2022	2021	2020
		(in thousands)	
Stock options	$ 54,971	$ 78,516	$ 90,064
Restricted stock units	5,587	25,375	4,904
Employee stock purchase plan	1,044	738	1,026
	$ 61,602	$ 104,629	$ 95,994

The stock-based compensation expense recorded for the restructuring in the year ended December 31, 2020 is the incremental amount related to modifying the exercise period for outstanding, vested stock option grants that had been granted to employees whose employment was terminated in the restructuring.

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 stock options are granted. The fair value of the stock options is

amortized on a straight-line basis for stock option awards to employees, non-employee directors and non-employee consultants 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, 2022, 2021 and 2020 was $25.96, $51.87 and $37.53, respectively.

The fair value of each stock option granted under the Company's equity plans has been calculated on the date of grant using the following weighted average assumptions:

	Year Ended December 31,		
	2022	2021	2020
Expected dividend yield	0%	0%	0%
Expected volatility	73%	76%	78%
Risk-free interest rate	2.49%	0.63%	0.97%
Expected term	6.03 years	5.92 years	5.98 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: effective January 1, 2020, the Company began using the historical volatility of only its common stock, as there is adequate historical data for the duration of the expected term.

Expected term (in years): the expected term represents the period that the Company's stock option grants are expected to be outstanding. The expected term of the stock options granted to employees, non-employee directors and non-employee consultants by the Company has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" stock options. Under this approach, the weighted average expected life is presumed to be the average of the vesting term and the contractual term of the stock option. This approach is used because the Company does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term due to the limited period of time that its stock has been publicly traded.

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 terminations. For the years ended December 31, 2022, 2021 and 2020, the weighted-average forfeiture rates were 19.2%, 16.7% and 20.6%, respectively.

2014 Employee Stock Purchase Plan

On July 2, 2014, the Company's stockholders approved the 2014 Employee Stock Purchase Plan (the "ESPP"), which had been previously approved by the Board. The ESPP became effective upon the completion of the IPO. A total of 282,000 shares of common stock were authorized for issuance under the ESPP.

On June 16, 2022, the Company's stockholders approved an amendment to the ESPP to add 300,000 shares of common stock to the ESPP.

As of December 31, 2022, 281,877 shares have been issued and 300,123 shares are available for issuance under the ESPP. At December 31, 2022, accrued expenses includes $0.8 million of stock-based compensation expense related to an enrollment period for which the related shares had not been issued as of December 31, 2022.

10. Net Income (Loss) Per Share

The following table shows the calculation of basic and diluted net income (loss) per share for the years ended December 31, 2022, 2021 and 2020:

	Year Ended December 31,		
	2022	2021	2020
Basic net income (loss) per share:			
Numerator:			
Net income (loss) (in thousands)	$ (532,784)	$ (457,892)	$ 606,073
Denominator:			
Weighted average common stock outstanding —basic	59,306,094	58,670,230	51,983,188
Effect of dilutive securities:			
Stock options	—	—	721,791
Restricted stock units	—	—	292,241
Employee Stock Purchase Plan	—	—	5,895
Total dilutive securities	—	—	1,019,927
Weighted average common stock outstanding —diluted	59,306,094	58,670,230	53,003,115
Net income (loss) per share—basic	$ (8.98)	$ (7.80)	$ 11.66
Net income (loss) per share—diluted	$ (8.98)	$ (7.80)	$ 11.43

The following table summarizes common stock equivalents outstanding that were excluded from the calculation of diluted net loss per share because including them would have been anti-dilutive as of December 31, 2022, 2021 and 2020:

	Year Ended December 31,		
	2022	2021	2020
Stock options	7,138,350	6,599,429	4,781,737
Restricted stock units	160,403	563,334	—
Employee stock purchase plan	76,105	23,625	—
	7,374,858	7,186,388	4,781,737

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

Income (loss) before income tax expense consists of the following:

	Year Ended December 31,		
	2022	2021	2020
		(in thousands)	
Domestic	$ (532,539)	$ (457,693)	$ 639,986
Foreign	(245)	(199)	(33,913)
	$ (532,784)	$ (457,892)	$ 606,073

There is no current or deferred provision for income taxes because the Company has historically incurred and utilized operating losses prior to the year ended December 31, 2022. As of December 31, 2022, the Company continues to maintain 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 the valuation allowance.

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

	Year Ended December 31,		
	2022	2021	2020
Tax due at statutory rate	21.0%	21.0%	21.0%
State taxes, net of federal	1.8	1.9	5.7
Biogen transaction-related items	—	—	(10.1)
Stock-based compensation	(1.9)	(5.2)	0.9
Foreign rate differential	—	—	1.2
Federal and state tax credits	2.1	3.5	(1.5)
Change in valuation allowance	(23.0)	(20.7)	(17.6)
Other	—	(0.5)	0.4
	0.0%	0.0%	0.0%

For the years ended December 31, 2022 and 2021, the impact from stock-based compensation on the Company's effective tax rate was primarily caused by shortfalls related to exercises and cancellations of non-qualified stock options.

For the year ended December 31, 2020, the Biogen transaction-related items consisted primarily of the excess proceeds from the equity investment under the Biogen Stock Purchase Agreement.

Significant components of the Company's net deferred tax assets at December 31, 2022 and 2021 are as follows:

	December 31,	
	2022	2021
	(in thousands)	
Net operating losses	$ 347,880	$ 305,824
Tax credits	118,393	106,176
Capitalized research and development expenses	66,849	—
Stock-based compensation	49,916	49,281
Accrued expenses	8,750	6,684
Depreciation and amortization	1,386	1,401
Right of use asset	(2,433)	(3,702)
Lease liability	2,803	4,236
Other	(258)	704
Total net deferred tax asset before valuation allowance	593,286	470,604
Valuation allowance	(593,286)	(470,604)
	$ —	$ —

On December 22, 2017, the Tax Cuts and Jobs Act (the "TCJA") was signed into law. Under the TCJA provisions, effective with tax years beginning on or after January 1, 2022, taxpayers can no longer immediately expense qualified research and development expenditures. Taxpayers are now required to capitalize and amortize these costs over five years for research conducted within the United States or 15 years for research conducted abroad. As a result, the Company capitalized $319.0 million of research and development expenses for the year ended December 31, 2022.

On August 16, 2022, the Inflation Reduction Act of 2022 (the "IRA") was signed into law. The IRA introduced new tax provisions, including a 15.0% corporate alternative minimum tax and a 1.0% excise tax on stock repurchases. The

provisions of the IRA will be effective for periods after December 31, 2022. The enactment of the IRA did not result in any material adjustments to our income tax provision or net deferred tax assets as of December 31, 2022.

As of December 31, 2022, the Company had federal net operating loss carryforwards of $1.5 billion, of which $30.2 million begin to expire in 2033 and the remainder do not expire but are subject to 80% limitation. As of December 31, 2022, the Company had state net operating loss carryforwards of $669.5 million that begin to expire in 2031. As of December 31, 2022, the Company had federal and state research and development tax credits carryforwards of $68.4 million and $12.5 million, respectively, which begin to expire in 2031 and 2027, respectively. As of December 31, 2022, the Company had federal orphan drug tax credit carryforwards of $40.1 million, which begin to expire in 2034.

As of December 31, 2022, net deferred tax assets before the valuation allowance increased $122.7 million, primarily due to the capitalization of research and development expenses and the increase of federal and state net operating loss carryforwards due to the loss generated for the year ended December 31, 2022. 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 federal and state net operating loss 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 its federal and state deferred tax assets. Accordingly, a full valuation allowance of $593.3 million and $470.6 million has been established at December 31, 2022 and 2021, respectively. The valuation allowance increased by $122.7 million for the year ended December 31, 2022, primarily due to the capitalization of research and development expenses and generation of net operating losses. The valuation allowance increased by $94.5 million and decreased by $107.2 million for the years ended December 31, 2021 and 2020, respectively, primarily due to generation or utilization of net operating losses.

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 and tax credit carryforwards that may be used in future years. Utilization of the net operating loss and tax credit carryforwards may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986, as amended, due to ownership change limitations that have occurred previously or that could occur in the future. These ownership changes may limit the amount of net operating loss and tax credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. The Company completed a Section 382 study through December 31, 2020. 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, the Company's net operating loss and tax credit carryforwards as of the ownership change dates are subject to limitation under Section 382; however, these limitations are not expected to cause any of the impacted net operating loss and tax credit carryforwards to expire unused. Any net operating losses 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 and tax credit carryforwards that could be utilized to offset future taxable income and tax.

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 table reconciles the beginning and ending amounts of gross unrecognized tax benefits, excluding interest and penalties, if any, for the years ended December 31, 2022 and 2021:

	2022	2021
	(in thousands)	
Balance as of January 1	$ 6,084	$ -
Increases related to current year tax positions	697	396
Increases related to prior year tax positions	65	5,688
Balance as of December 31	$ 6,846	$ 6,084

For the years ended December 31, 2022 and 2021, the increases in unrecognized tax benefits related to current year and prior year tax positions primarily related to the Company's federal and state tax credits.

The Company's policy is to record interest and penalties related to income taxes as part of the tax provision. As of December 31, 2022 and 2021, the Company had no accrued interest or penalties related to income taxes and no amounts have been recognized in the Company's statements of operations and comprehensive income (loss) for the years ended December 31, 2022, 2021 and 2020.

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, state and foreign jurisdictions, where applicable. There are currently no pending tax examinations, and the Company's tax returns are generally open under statute from 2019 to the present. Tax attributes such as net operating losses and tax credits generated prior to 2019 and utilized in open years may still be adjusted upon examination.

12. Employee Benefit Plan

The Company maintains a 401(k) profit sharing plan (the "401(k) Plan") for its employees. Each employee may elect to contribute a portion of his or her compensation to the 401(k) Plan, subject to annual limits established by the Internal Revenue Service. For the years ended December 31, 2022, 2021 and 2020, the Company matched 50% of eligible contributions to the 401(k) Plan up to 6% of employee contributions. For the years ended December 31, 2022, 2021 and 2020 the Company contributed $3.0 million, $1.8 million and $2.2 million, respectively, to the 401(k) Plan.

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	Amended and Restated Bylaws of the Registrant, as amended on August 6, 2020 (incorporated by reference to Exhibit 3.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on August 10, 2020)
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	Description of Securities (incorporated by reference to Exhibit 4.2 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on February 27, 2020)
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**	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)
10.3**	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)
10.4	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)
10.5+	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)
10.6+	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)
10.7+	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)
10.8+	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)
10.9+	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)

Exhibit No.	Description
10.10+	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)
10.11	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)
10.12	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)
10.13**	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)
10.14+	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)
10.15+*	Severance and Change In Control Agreement between the Registrant and Kimi Iguchi, dated September 30, 2014, as amended
10.16+*	Severance and Change In Control Agreement between the Registrant and Albert J. Robichaud, dated September 25, 2014, as amended
10.17**	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)
10.18	Third Amendment to Lease, by and between Registrant and ARE-MA Region No. 38, LLC, dated 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)
10.19	Fourth Amendment to Lease, by and between the Registrant and ARE-MA Region No. 38, LLC, dated 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)
10.20	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)
10.21	Fifth Amendment to Lease, by and between the Registrant and ARE-MA Region No. 38, LLC, dated 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)
10.22	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)
10.23+	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
10.24	Sixth Amendment to Lease by and between ARE-MA Region No. 38, LLC and the Registrant, dated 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)
10.25	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)
10.26+	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)
10.27	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)
10.28	Eighth Amendment to Lease by and between ARE-MA Region No. 38, LLC and the Registrant, dated March 29, 2019 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on August 6, 2019)
10.29+	Form of Performance-Based Restricted Stock Unit Award Agreement Under the Sage Therapeutics, Inc. 2014 Stock Option and Incentive Plan (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on August 10, 2020)
10.30*†	Biogen Collaboration and License Agreement by and among the Registrant, Biogen MA Inc. and Biogen International GmbH, dated November 27, 2020
10.31†	Stock Purchase Agreement by and between the Registrant and Biogen MA Inc., dated November 27, 2020 (incorporated by reference to Exhibit 10.39 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on February 24, 2021)
10.32+	Offer Letter by and between the Registrant and Barry Greene, dated December 15, 2020 (incorporated by reference to Exhibit 10.40 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on February 24, 2021)
10.33+	Severance and Change In Control Agreement between the Registrant and Barry Greene, dated December 15, 2020 (incorporated by reference to Exhibit 10.41 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on February 24, 2021)
10.34+	Letter Agreement between the Registrant and Jeffrey Jonas, dated December 15, 2020 (incorporated by reference to Exhibit 10.42 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on February 24, 2021)
10.35+	Offer Letter by and between the Registrant and Christopher Benecchi, dated September 13, 2021 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on November 2, 2021)
10.36+*	Severance and Change In Control Agreement between the Registrant and Christopher Benecchi, dated September 13, 2021, as amended
10.37	Side Letter to Biogen Collaboration and License Agreement, by and among the Registrant, Biogen MA Inc. and Biogen International GmbH, dated October 21, 2021 (incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on November 2, 2021)
10.38+	2014 Employee Stock Purchase Plan, as amended, dated June 16, 2022 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on August 2, 2022)
10.39+*	Offer Letter by and between the Registrant and Laura Gault, dated October 18, 2022
10.40+*	Severance and Change in Control Agreement between the Registrant and Laura Gault, dated October 18, 2022, as amended
10.41+*	CNS Innovation Advisory Board Consulting Agreement between the Registrant and Jeff Jonas, dated November 8, 2022
10.42+*	Amended and Restated Non-Employee Director Compensation Policy, dated December 16, 2022

Exhibit No.	Description
21.1*	Subsidiaries of the Registrant
23.1*	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm
24.1*	Power of Attorney (see signature page of this Annual Report on Form 10-K)
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*	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document)
101.SCH*	Inline XBRL Taxonomy Extension Schema Document
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104*	Cover Page Interactive Data File (formatted as inline XBRL and contained in Exhibit 101.*)

(+) Management contract or compensatory plan or arrangement.

(*) Filed herewith.

(**) 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.

(†) Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

SIGNATURES

Pursuant to the requirements of 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 16, 2023

By: /s/ Barry E. Greene

Barry E. Greene
Chief Executive Officer, President and Director
(Principal Executive Officer)

We, the undersigned directors and officers of Sage Therapeutics, Inc., hereby severally constitute and appoint Barry E. Greene and Kimi Iguchi, and each of them singly, our true and lawful attorneys-in-fact, with full power to them, and to each of them singly, to sign for us and in our names in the capacities indicated below, any and all amendments to this Annual Report on Form 10-K, and to file or cause to be filed the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as each of us might or could do in person, and hereby ratifying and confirming all that said attorneys-in-fact, and each of them, or their substitute or substitutes, shall do or cause to be done by virtue of this power of attorney.

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/ Barry E. Greene Barry E. Greene	Chief Executive Officer, President and Director (Principal Executive Officer)	February 16, 2023
/s/ Kimi Iguchi Kimi Iguchi	Chief Financial Officer (Principal Financial and Accounting Officer)	February 16, 2023
/s/ Jeffrey M. Jonas Jeffrey M. Jonas, M.D.	Director	February 16, 2023
/s/ Michael F. Cola Michael F. Cola	Director	February 16, 2023
/s/ Steven Paul Steven Paul, M.D.	Director	February 16, 2023
/s/ Kevin P. Starr Kevin P. Starr	Director	February 16, 2023
/s/ James Frates James Frates	Director	February 16, 2023
/s/ Geno Germano Geno Germano	Director	February 16, 2023
/s/ Elizabeth Barrett Elizabeth Barrett	Director	February 16, 2023
/s/ George Golumbeski George Golumbeski, Ph.D.	Director	February 16, 2023

Building a business for the future

DEEP EXPERTISE IN BRAIN CIRCUITRY

12 Years Since Founding

RICH INNOVATIVE PIPELINE

3 Late Stage Programs

6 NCE development programs across 11+ potential indications

SIGNIFICANT POTENTIAL PATIENT IMPACT

+450 Million patients to potentially impact

EXCITING BUSINESS MOMENTUM INTO 2023

EXECUTIVE LEADERSHIP

Barry Greene
Chief Executive Officer

Chris Benecchi
Chief Business Officer

Helen Colquhoun
SVP, Drug Safety and Pharmacovigilance

Anne Marie Cook
SVP, General Counsel

Jim Doherty, Ph.D.
Chief Development Officer

Laura Gault, M.D., Ph.D.
Chief Medical Officer

Kimi Iguchi
Chief Financial Officer

Erin Lanciani
Chief People and Experience Officer

Matt Lasmanis
Chief Technology and Innovation Officer

Tammy Phinney
SVP, Regulatory Affairs

Mark Pollack, M.D.
SVP, Global Medical Affairs

Vanessa Proctor
SVP, External Affairs

Mike Quirk, Ph.D.
SVP, Discovery Research

Al Robichaud, Ph.D.
Chief Scientific Officer

Abdul Sankoh, Ph.D., FASA
SVP, Data Science

Amy Schacterle, Ph.D.
SVP, R&D Strategy and Business Management

Heinrich Schlieker, Ph.D.
SVP, Technical Operations

BOARD OF DIRECTORS

Barry Greene
Liz Barrett
Michael F. Cola
Jessica Federer
James M. Frates
Geno Germano
George Golumbeski, Ph.D.
Jeff Jonas, M.D.
Steven Paul, M.D.
Kevin Starr

Biographies for the members of our board of directors are contained under the heading "Biographical Information Concerning Our Board of Directors" in our proxy statement for the 2023 annual meeting of stockholders, which has been made available to stockholders with this Annual Report.

Sage Therapeutics is a biopharmaceutical company committed *to developing novel therapies with the potential to transform the lives of people with debilitating disorders of the brain.*

CORPORATE HEADQUARTERS
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(617) 299–8380

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ThisIsSage
@sagebiotech

Sage Therapeutics®