UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-Q

(Mark One)

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

For the quarterly period ended June 30, 2019

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 **(State or other jurisdiction of incorporation or organization)**	**27-4486580** **(I.R.S. Employer Identification No.)**

215 First Street
Cambridge, Massachusetts 02142
(Address of principal executive office) (Zip Code)

Registrant's telephone number, including area code: (617) 299-8380

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

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 (§ 232.405 of this chapter) 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 is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

As of July 31, 2019, there were 51,656,993 shares of the registrant's common stock, $0.0001 par value per share, outstanding.

Cautionary Note Regarding Forward-Looking Statements

This Quarterly Report on Form 10-Q, or Quarterly 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 Quarterly 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 view as to potential future results of our ongoing commercialization efforts in the U.S. with respect to ZULRESSO™ (brexanolone) injection which is approved in the U.S. for the treatment of postpartum depression, or PPD, including our expectations with respect to: future revenues and sales momentum; the number of patients who may receive ZULRESSO for the treatment of PPD; the availability and willingness of healthcare settings to administer ZULRESSO; the scope, level and availability of reimbursement, including reimbursement for costs incurred by the healthcare settings that administer ZULRESSO, reimbursement of cost of treatment to the patient, and the nature of any limitations imposed by payors; and the level of market acceptance of ZULRESSO as a treatment for PPD by healthcare settings, prescribers and women suffering from PPD.
- our expectations as to the sufficiency of our planned development program for SAGE-217 in major depressive disorder and PPD, if successful, to support filing of a New Drug Application, or NDA, with the FDA; our statements regarding the potential for approval of SAGE-217 in such indications in the U.S.; our plans and expectations for development of SAGE-217 in additional indications; our plans and expectations for commercialization of SAGE-217 and our view of the potential product profile, market impact, market size and opportunity for SAGE-217, if successfully developed and approved.
- our plans to develop SAGE-324, SAGE-718 and our other product candidates in the central nervous system, or CNS, disorders we discuss in this Quarterly Report, and potentially in other indications and our view of the potential product profile and treatment paradigm impact for such product candidates, if successfully developed and approved;
- our ability, within the expected time-frames, to initiate clinical trials and non-clinical studies of existing or future product candidates, including pivotal clinical trials, and to successfully complete and announce the results of ongoing or future clinical trials;
- our plans and potential outcomes with respect to other research and development activities and our 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 estimates regarding expenses, use of cash and projected cash on hand at any given timepoint, timing of future cash needs, and capital requirements;
- our expectations as to the amount of future revenues that may be achieved;
- our expectations with respect to the availability of supplies of ZULRESSO and our product candidates, and the expected performance of our third-party manufacturers;
- our ability to obtain and maintain intellectual property protection for our proprietary assets and other forms of exclusivity relevant to our business;

- the estimated number of patients with diseases or disorders of interest to us; the potential size of the market for ZULRESSO in PPD and for our product candidates in the indications we are studying or plan to study; the potential for ZULRESSO as a treatment for PPD and current or future product candidates, if successfully developed and approved, in the markets for which they are approved; and our ability to serve those markets;
- the level of costs we may incur in connection with our activities, the possible timing and sources of future financings, and our ability to obtain additional financing when needed to fund future operations;
- the potential for success of competing products that are or become available for PPD or any of the indications that we are pursuing or may pursue in the future with our product candidates;
- the potential risk of loss of key scientific or management personnel; and
- other risks and uncertainties, including those listed under Part II, Item 1A, Risk Factors.

Any forward-looking statements in this Quarterly 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 II, Item 1A, Risk Factors and elsewhere in this Quarterly Report. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

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

Sage Therapeutics, Inc.

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PART I — FINANCIAL INFORMATION

Item 1. Financial Statements

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

	June 30, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 166,185	$ 190,943
Marketable securities	1,070,364	731,833
Prepaid expenses and other current assets	27,021	21,919
Total current assets	1,263,570	944,695
Property and equipment, net	8,363	5,643
Restricted cash	2,367	2,367
Right of use operating asset	37,224	—
Other long-term assets	4,023	—
Total assets	$ 1,315,547	$ 952,705
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 12,431	$ 34,036
Accrued expenses	58,912	51,994
Other current liabilities	7,610	—
Total current liabilities	78,953	86,030
Long-term lease operating liability, net of current portion	33,309	—
Other long-term liabilities	410	3,704
Total liabilities	112,672	89,734
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, $0.0001 par value per share; 5,000,000 shares authorized at June 30, 2019 and December 31, 2018; no shares issued or outstanding at June 30, 2019 and December 31, 2018	—	—
Common stock, $0.0001 par value per share; 120,000,000 shares authorized at June 30, 2019 and December 31, 2018; 51,472,137 and 46,891,296 shares issued at June 30, 2019 and December 31, 2018; 51,469,104 and 46,888,263 shares outstanding at June 30, 2019 and December 31, 2018	5	5
Treasury stock, at cost, 3,033 shares at June 30, 2019 and December 31, 2018	(400)	(211)
Additional paid-in capital	2,496,651	1,827,021
Accumulated deficit	(1,294,956)	(963,329)
Accumulated other comprehensive gain (loss)	1,575	(515)
Total stockholders' equity	1,202,875	862,971
Total liabilities and stockholders' equity	$ 1,315,547	$ 952,705

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Product revenue, net	$ 519	$ —	$ 519	$ —
Collaboration revenue	354	90,000	819	90,000
Total revenue	873	90,000	1,338	90,000
Operating costs and expenses:				
Cost of goods sold	44	—	44	—
Research and development	89,059	68,980	175,457	118,250
Selling, general and administrative	88,227	43,167	172,146	72,016
Total operating costs and expenses	177,330	112,147	347,647	190,266
Loss from operations	(176,457)	(22,147)	(346,309)	(100,266)
Interest income, net	8,220	5,137	14,662	8,666
Other income, net	16	32	20	24
Net loss	$ (168,221)	$ (16,978)	$ (331,627)	$ (91,576)
Net loss per share—basic and diluted	$ (3.28)	$ (0.36)	$ (6.65)	$ (2.02)
Weighted average number of common shares outstanding—basic and diluted	51,257,640	46,541,716	49,882,377	45,439,666
Comprehensive loss:				
Net loss	$ (168,221)	$ (16,978)	$ (331,627)	$ (91,576)
Other comprehensive items:				
Unrealized gain (loss) on marketable securities	1,681	40	2,090	(116)
Total other comprehensive gain (loss)	1,681	40	2,090	(116)
Total comprehensive loss	$ (166,540)	$ (16,938)	$ (329,537)	$ (91,692)

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

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

	Six Months Ended June 30,	
	2019	2018
Cash flows from operating activities		
Net loss	$ (331,627)	$ (91,576)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	78,883	44,845
Premium on marketable securities	(1,887)	(75)
Amortization of discount on marketable securities	(4,973)	(4,154)
Depreciation	920	493
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(5,102)	(25,091)
Other long-term assets	(4,023)	—
Right of use operating asset	4,713	—
Operating lease liabilities	(4,346)	—
Accounts payable	(21,806)	(903)
Accrued expenses and other liabilities	5,970	(2,245)
Net cash used in operating activities	(283,278)	(78,706)
Cash flows from investing activities		
Proceeds from sales and maturities of marketable securities	588,652	263,460
Purchases of marketable securities	(918,233)	(813,337)
Purchases of property and equipment	(3,438)	(1,054)
Net cash used in investing activities	(333,019)	(550,931)
Cash flows from financing activities		
Proceeds from stock option exercises and employee stock purchase plan issuances	31,282	19,402
Payment of employee tax obligations related to vesting of restricted stock units	(692)	(904)
Payments of offering costs	(328)	(340)
Proceeds from public offerings of common stock, net of commissions and underwriting discounts	561,277	631,494
Net cash provided by financing activities	591,539	649,652
Net increase (decrease) in cash, cash equivalents and restricted cash	(24,758)	20,015
Cash, cash equivalents and restricted cash at beginning of period	193,310	307,084
Cash, cash equivalents and restricted cash at end of period	$ 168,552	$ 327,099
Supplemental disclosure of non-cash operating and investing activities		
Purchases of property and equipment included in accounts payable	$ 252	$ 10
Right of use assets obtained in exchange for new operating lease liabilities	$ 872	$ —

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

Sage Therapeutics, Inc. and Subsidiaries
Consolidated Statements of Changes in Stockholders' Equity
(in thousands, except share data)
(Unaudited)

	Common Stock		Treasury Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount	Shares	Amount				
Balances at December 31, 2017	42,002,934	$ 5	960	$ (113)	$ 1,066,059	$ (29)	$ (590,447)	$ 475,475
Issuance of common stock from exercise of stock options	402,227	—	—	—	11,727	—	—	11,727
Issuance of common stock under employee stock purchase plan	11,683	—	—	—	1,127	—	—	1,127
Purchase of treasury stock	—	—	554	(98)	—	—	—	(98)
Stock-based compensation expense	—	—	—	—	15,549	—	—	15,549
Public offering of common stock, net of offering costs	4,032,012	—	—	—	631,154	—	—	631,154
Unrealized loss on available-for-sale securities	—	—	—	—	—	(156)	—	(156)
Vesting of restricted stock units, net of employee tax obligations	9,442	—	—	—	(904)	—	—	(904)
Net loss	—	—	—	—	—	—	(74,598)	(74,598)
Balances at March 31, 2018	46,458,298	$ 5	1,514	$ (211)	$ 1,724,712	$ (185)	$ (665,045)	$ 1,059,276
Issuance of common stock from exercise of stock options	145,541	—	—	—	6,643	—	—	6,643
Stock-based compensation expense	—	—	—	—	28,782	—	—	28,782
Unrealized loss on available-for-sale securities	—	—	—	—	—	40	—	40
Net loss	—	—	—	—	—	—	(16,978)	(16,978)
Balances at June 30, 2018	46,603,839	$ 5	1,514	$ (211)	$ 1,760,137	$ (145)	$ (682,023)	$ 1,077,763
Balances at December 31, 2018	46,888,263	$ 5	3,033	$ (211)	$ 1,827,021	$ (515)	$ (963,329)	$ 862,971
Issuance of common stock from exercise of stock options	287,659	—	—	—	14,072	—	—	14,072
Issuance of common stock under employee stock purchase plan	16,398	—	—	—	1,799	—	—	1,799
Purchase of treasury stock	—	—	—	(189)	—	—	—	(189)
Stock-based compensation expense	—	—	—	—	43,622	—	—	43,622
Public offering of common stock, net of offering costs	3,833,334	—	—	—	560,948	—	—	560,948
Unrealized gain on available-for-sale securities	—	—	—	—	—	409	—	409
Vesting of restricted stock units, net of employee tax obligations	8,518	—	—	—	(692)	—	—	(692)
Net loss	—	—	—	—	—	—	(163,406)	(163,406)
Balances at March 31, 2019	51,034,172	$ 5	3,033	$ (400)	$ 2,446,770	$ (106)	$ (1,126,735)	$ 1,319,534
Issuance of common stock from exercise of stock options	434,932	—	—	—	15,601	—	—	15,601
Stock-based compensation expense	—	—	—	—	34,280	—	—	34,280
Unrealized gain on available-for-sale securities	—	—	—	—	—	1,681	—	1,681
Net loss	—	—	—	—	—	—	(168,221)	(168,221)
Balances at June 30, 2019	51,469,104	$ 5	3,033	$ (400)	$ 2,496,651	$ 1,575	$ (1,294,956)	$ 1,202,875

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

1. Nature of the Business

Sage Therapeutics, Inc. (“Sage” or the “Company”) is a biopharmaceutical company committed to developing and commercializing novel medicines with the potential to transform the lives of people with debilitating disorders of the brain. The Company’s lead product, ZULRESSO™ (brexanolone) injection, was approved by the U.S. Food and Drug Administration (“FDA”) in March 2019, for the treatment of postpartum depression (“PPD”) in adults, and was made commercially available in the U.S. beginning on June 24, 2019 after completion of controlled substance scheduling of brexanolone by the U.S. Drug Enforcement Administration and incorporation of the scheduling into the FDA-approved label and other product information. The Company has a portfolio of other product candidates with a current focus on modulating two critical CNS receptor systems, GABA and NMDA. The GABA receptor family, which is recognized as the major inhibitory neurotransmitter in the CNS, mediates downstream neurologic and bodily function via activation of GABAA receptors. The NMDA-type receptors of the glutamate receptor system are a major excitatory receptor system in the CNS. Dysfunction in these systems is implicated in a broad range of CNS disorders. The Company is targeting CNS indications where patient populations are easily identified, clinical endpoints are well-defined, and development pathways are feasible.

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

The Company is subject to risks and uncertainties common to companies in the biotech and pharmaceutical 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 commercializing pharmaceutical products for marketing and sale; the potential for development by third parties of new technological innovations that may compete with the Company’s products; the dependence on key personnel; the challenges of protecting proprietary technology; the need to comply with government regulations; the high costs of drug development; and the uncertainty of being able to secure additional capital when needed to fund operations.

Under Accounting Standards Update (“ASU”) 2014-15, *Presentation of Financial Statements—Going Concern* (Subtopic 205-40), or ASC 205-40, the Company has the responsibility to evaluate whether conditions and/or events raise substantial doubt about its ability to meet its future financial obligations as they become due within one year after the date that the financial statements are issued. The Company has incurred losses and negative cash flows from operations since its inception. As of June 30, 2019, the Company had an accumulated deficit of $1.3 billion. From its inception through June 30, 2019, the Company received net proceeds of $2.2 billion from the sales of redeemable convertible preferred stock, the issuance of convertible notes, and the sales of common stock in its initial public offering (“IPO”) in July 2014 and follow-on public offerings in April 2015, January 2016, September 2016, November 2017, February 2018, and February 2019. Until such time, if ever, as the Company can generate substantial product revenue and achieve profitability, the Company expects to finance its cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other sources of funding. If the Company is unable to raise additional funds through equity or debt financings when needed, the Company may be required to delay, limit, reduce or terminate product development or future commercialization efforts or grant rights to develop and market products or product candidates that the Company would otherwise prefer to develop and market itself. The Company expects that, based on its current operating plans, the Company’s existing cash, cash equivalents and marketable securities will be sufficient to fund its current planned operations for at least the next twelve months from the issuance of these unaudited interim condensed consolidated financial statements. At some point after that time, the Company will require additional financing to fund its future operations.

2. Summary of Significant Accounting Policies

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

Basis of Presentation

The unaudited interim condensed consolidated financial statements of the Company included herein have been prepared pursuant to the rules and regulations of the Securities and Exchange Commission (the "SEC"). Certain information and footnote disclosures normally included in financial statements prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") have been condensed or omitted from this report, as is permitted by such rules and regulations. Accordingly, these unaudited condensed consolidated financial statements should be read in conjunction with the audited consolidated financial statements as of and for the year ended December 31, 2018, included in the Company's Annual Report on Form 10-K for the year ended December 31, 2018.

The unaudited interim condensed consolidated financial statements have been prepared on the same basis as the audited consolidated financial statements. In the opinion of the Company's management, the accompanying unaudited condensed consolidated financial statements contain all adjustments, consisting of only normal recurring adjustments, necessary for a fair statement of its financial position as of June 30, 2019, its results of operations and comprehensive loss for the three and six months ended June 30, 2019 and 2018, its cash flows for the six months ended June 30, 2019 and 2018, and its statements of changes in stockholders' equity for the six months ended June 30, 2019 and 2018. The consolidated balance sheet at December 31, 2018 was derived from audited financial statements, but does not include all disclosures required by GAAP. The results for the three and six months ended June 30, 2019 are not necessarily indicative of the results for the year ending December 31, 2019, or for any future period.

Principles of Consolidation

The unaudited interim condensed consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries as disclosed in Note 2, Summary of Significant Accounting Policies, within the "Notes to Consolidated Financial Statements" accompanying its Annual Report on Form 10-K for the fiscal year ended December 31, 2018. 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. Actual results could differ from those estimates.

Research and Development

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

The Company has entered into various research and development contracts with research institutions and other companies both inside and outside of the 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 evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates may be made in determining the accrued balances at the end of any reporting period. Actual results could differ from the estimates made by the Company. The historical accrual estimates made by the Company have not been materially different from the actual costs.

Stock-Based Compensation

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

Effective January 1, 2019, the Company recognizes compensation expense for stock-based awards, including grants of stock options and restricted stock, made to non-employee consultants based on the estimated fair value on the date of grant, over the requisite service period. Through December 31, 2018, the Company recognized compensation expense for stock-based awards granted to non-employee consultants based on the fair value of the awards on each date on which the awards vest. Compensation expense was recognized over the vesting period, provided that services were rendered by such non-employee consultants during that time. At the end of each financial reporting period, the fair value of unvested options was re-measured using the then-current fair value of the common stock of the Company and updated assumptions in the Black-Scholes option-pricing model.

For awards that vest upon achievement of a performance condition, the Company recognizes compensation expense when achievement of the performance condition is met or during the period from which meeting the condition is deemed probable until the expected date of meeting the performance condition.

The fair value of each option grant is estimated using the Black-Scholes option-pricing model. Through December 31, 2015, the Company lacked sufficient Company-specific historical and implied volatility information, and as a result, the Company used the volatility of a group of publicly-traded peer companies in the Black-Scholes calculations. Beginning in 2016, the Company estimated its expected volatility using a weighted average of the historical volatility of publicly-traded peer companies and the volatility of its common stock and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its traded stock price for the duration of the expected term. The expected term of the options granted to employees and non-employee directors by the Company has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. Through December 31, 2018, the expected term of its options granted to non-employee consultants has been determined based on the contractual term of the options, and effective January 1, 2019, the "simplified" method is used. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. The expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

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

Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity of 90 days or less at the date of purchase to be cash equivalents. As of June 30, 2019 and December 31, 2018, cash equivalents were comprised of cash equivalents and money market funds.

Marketable securities

Marketable securities consist of investments with original maturities greater than 90 days. The Company has classified its investments with maturities beyond one year as short-term, based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. The Company considers its investment portfolio of investments to be available-for-sale. Accordingly, these investments are recorded at fair value, which is based on quoted market prices. Unrealized gains and losses are reported as a component of accumulated other comprehensive items in stockholders' equity. Realized gains and losses and declines in value judged to be other than temporary are included as a component of other expense, net, based on the specific identification method. When determining whether a decline in value is other than temporary, the Company considers several factors, including whether the Company has the intent to sell the security, and whether it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis. No declines in value were deemed to be other than temporary during the three and six months ended June 30, 2019 and 2018.

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 June 30, 2019 and December 31, 2018 were carried at fair value, determined according to the fair value hierarchy; see Footnote 3, Fair Value Measurements herein.

The carrying amounts reflected in the unaudited condensed consolidated balance sheets for accounts payable and accrued expenses approximate their fair values due to their short-term maturities at June 30, 2019 and December 31, 2018, respectively.

Revenue Recognition

Effective January 1, 2017, the Company adopted Accounting Standards Codification ("ASC"), Topic 606, *Revenue from Contracts with Customers* ("Topic 606"). This standard applies to all contracts with customers, except for contracts that may be within the scope of other standards, such as collaboration arrangements and leases. The adoption of Topic 606 had no impact on the Company's consolidated financial statements as the Company did not have any revenue prior to adoption.

The Company received approval of ZULRESSO from the FDA in March 2019 and subsequently began to record revenues from product sales in June 2019. Prior to the second quarter of 2019, all of the revenues of the Company were derived from the Company's collaboration agreement with Shionogi & Co., Ltd., ("Shionogi"). The terms of the Company's collaboration agreement include consideration such as non-refundable license fees, funding of research and development services, payments due upon the achievement of clinical and pre-clinical performance-based development milestones, regulatory milestones, manufacturing services to supply drug product for clinical trials, and sales-based milestones and royalties on product sales.

Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(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. 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 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 arrangement with Shionogi and concluded that a significant financing component does not exist. For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time this is based on the use of an output or input method. To date, revenue from the Company’s collaboration agreement with Shionogi has come from an initial, up-front fee upon execution of the agreement and payment for the supply of SAGE-217 drug product for Shionogi clinical trials.

Product revenue

The Company recognizes product revenues, 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 delivery is made and 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 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 June 30, 2019, as customer invoicing generally occurs before or at the time of revenue recognition. The Company did not have any contract liabilities at June 30, 2019, as the Company did not receive any payments in advance of satisfying its performance obligations to its customers. Amounts billed or invoiced are included in prepaid expenses and other current assets on the consolidated balance sheets.

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 will update its estimates and record any necessary 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 fees and discounts resulting from contractual commitments to sell products to qualified healthcare providers 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 qualified healthcare providers. 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 qualified healthcare providers, 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 revenues and a current liability that is included in accrued expenses on its consolidated balance sheet. 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 revenues and accounts receivable at the time the Company recognizes the related revenues.

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 average financial assistance amounts for ZULRESSO based on demographics for patients who have registered and been approved for assistance and records any such amounts within accrued expenses on its consolidated balance sheet. 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 associated with product that has been recognized as revenue but remains in the distribution channel at the end of each reporting period, as well as claims that have been approved but not yet paid. The 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 and other current liabilities on the consolidated balance sheets.

Product Returns: Consistent with industry practice, the Company offers the specialty pharmacies and specialty distributors that are its customers limited product return rights for damaged, defective or expiring product, provided it is within a specified period around the product expiration date as set forth in the applicable individual distribution agreement. 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. Based on the distribution model for ZULRESSO, contractual inventory limits with its customers, the product price and limited contractual return rights, the Company believes there will be minimal ZULRESSO returns. The Company will update its estimated refund liability, on at least a quarterly basis, based on actual shipments of ZULRESSO subject to contractual return rights, changes in expectations about the amount of estimated refunds or actual returns.

Inventory

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 are identical and, as a result, are both classified as inventory. Amounts in inventory associated with research and development 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 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 loss. Inventory on-hand that will be sold beyond the Company's normal operating cycle is classified as non-current and grouped with other assets on the Company's consolidated balance sheets. At June 30, 2019, the Company did not have any such inventory.

Prior to the initial date regulatory approval is received, costs related to the production of inventory are recorded as research and development expense on the Company’s consolidated statements of operations and comprehensive loss in the period incurred. The Company received FDA approval for ZULRESSO on March 19, 2019 and subsequently began capitalizing costs related to inventory manufacturing.

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 revenues 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 on March 19, 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 current period.

Accounts Receivable

The Company’s trade accounts receivable consist of amounts due from specialty distributors and specialty pharmacies in the U.S. related to sales of ZULRESSO and have standard payment terms that generally require payment within 30 to 60 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 profile. The Company reserves against trade accounts receivable for estimated losses that may arise from a customer’s inability to pay and any amounts determined to be uncollectible are written off against the reserve when it is probable that the receivable will not be collected. Trade accounts receivable are included in prepaid expenses and other current assets on the consolidated balance sheets and the amount was not significant as of June 30, 2019.

Intangible assets

The Company had no intangible assets as of December 31, 2018. As a result of the approval by the FDA of the New Drug Application for ZULRESSO in March 2019, the Company was required to pay to CyDex Pharmaceuticals, Inc. ("CyDex") and The Regents of the University of California milestone payments of $3.0 million and $0.5 million, respectively. At March 31, 2019, the amount of these milestones was capitalized as an intangible asset, and no amounts had been amortized. During the three months ended June 30, 2019, the Company began to amortize the asset and record the expense to cost of goods sold.

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 lease 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 that option. The Company uses the implicit interest rate when readily determinable and uses the Company's incremental borrowing rate when the implicit rate is not readily determinable based upon the information available at the commencement date in determining the present value of the lease payments.

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 condensed consolidated balance sheets. In addition, the Company's contracts 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 right of use operating asset, other current liabilities and long-term lease operating liability, net of current portion in the Company's condensed 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 excluded from this treatment and are recognized on a straight-line basis over the term of the lease.

Recently Issued Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board ("FASB") issued ASU No. 2016-02, *Leases*, which replaced the existing guidance in ASC 840, "Leases", and in July 2018, the FASB issued ASU No. 2018-11, *Leases (Topic 842): Targeted Improvements* ("ASC 842"). The ASC 842 standard generally requires lessees to recognize operating and financing lease liabilities and corresponding right-of-use assets on the consolidated balance sheet and to provide enhanced disclosures surrounding the amount, timing and uncertainty of cash flows arising from leasing arrangements. The Company adopted ASC 842 using the modified retrospective approach with an effective date of January 1, 2019 for leases that existed on that date. Prior period results continue to be presented under ASC 840 based on the accounting standards originally in effect for such periods. Presentation of leases within the consolidated statements of operations and comprehensive loss and consolidated statements of cash flows is generally consistent with the former lease accounting guidance. The Company elected the package of practical expedients permitted under the transition guidance and as such, the adoption of this ASU did not change the classification of any of the Company's leases. The Company elected to combine lease and non-lease components, elected not to record leases with an initial term of 12 months or less on the balance sheet and will recognize the associated lease payments in the consolidated statements of operations and comprehensive loss on a straight-line basis over the lease term. On the implementation date, $44.2 million was recognized as total lease liabilities and $41.1 million was recognized as total right-of-use assets on the Company's consolidated balance sheet.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments*, which introduces a new methodology for accounting for credit losses on financial instruments, including available-for-sale debt securities. The guidance establishes a new "expected loss model" that requires entities to estimate current expected credit losses on financial instruments by using all practical and relevant information. Any expected credit losses are to be reflected as allowances rather than reductions in the amortized cost of available-for-sale debt securities. Early adoption is permitted for annual periods beginning after December 15, 2018, and interim periods therein. The Company adopted the standard on the required effective date of January 1, 2019. This guidance did not have a significant impact on the Company's consolidated financial statements and related disclosures.

In June 2018, the FASB issued ASU 2018-07, Compensation—Stock Compensation (Topic 718) – Improvements to Nonemployee Share-Based Payment Accounting ("ASU 2018-07"), which aligns the accounting for share-based payment awards issued to employees and non-employees. Under the new guidance, the existing guidance regarding employees will apply to share-based transactions with non-employees, as long as the transaction is not effectively a form of financing, with the exception of specific guidance related to the attribution of compensation cost. The cost of non-employee awards will continue to be recorded as if the grantor had paid cash for the goods or services. In addition, the contractual term will be able to be used in lieu of an expected term in the option-pricing model for non-employee awards. The Company adopted the standard on the required effective date of January 1, 2019. 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 of the fair value hierarchy. The Company's investments in marketable securities are classified within Level 2 of the fair value hierarchy.

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

The following tables summarize the Company's money market funds and marketable securities as of June 30, 2019 and December 31, 2018.

	June 30, 2019			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(in thousands)			
Cash equivalents:				
Cash equivalents	$ 166,185	$ 166,185	$ —	$ —
Total cash equivalents	166,185	166,185	—	—
Marketable securities:				
U.S. government securities	290,571	—	290,571	—
U.S. corporate bonds	478,806	—	478,806	—
International corporate bonds	147,470	—	147,470	—
U.S. commercial paper	107,099	—	107,099	—
International commercial paper	46,418	—	46,418	—
Total marketable securities	1,070,364	—	1,070,364	—
	$ 1,236,549	$ 166,185	$ 1,070,364	$ —

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

During the six months ended June 30, 2019 and 2018, 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 June 30, 2019 and December 31, 2018:

	June 30, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in thousands)			
Assets:				
U.S. government securities	$ 290,271	$ 302	$ (2)	$ 290,571
U.S. corporate bonds	477,932	942	(68)	478,806
International corporate bonds	147,062	434	(26)	147,470
U.S. commercial paper	107,105	1	(7)	107,099
International commercial paper	46,419	—	(1)	46,418
	$ 1,068,789	$ 1,679	$ (104)	$ 1,070,364

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

As of June 30, 2019, all marketable securities, except for 48 bonds with a fair value of $185.0 million that have maturities of between one and two years, held by the Company had remaining contractual maturities of one year or less. As of December 31, 2018, all marketable securities, except for two U.S. corporate bonds, held by the Company had remaining contractual maturities of one year or less.

There have been no impairments of the Company's assets measured and carried at fair value during the six months ended June 30, 2019 and the year ended December 31, 2018.

4. Balance Sheet Components

Property and Equipment, net

Property and equipment, net, consists of the following:

	June 30, 2019	December 31, 2018
	(in thousands)	
Computer hardware and software	$ 2,427	$ 2,148
Furniture and equipment	1,774	1,002
Leasehold improvements	7,298	4,709
	11,499	7,859
Less: Accumulated depreciation	(3,136)	(2,216)
	$ 8,363	$ 5,643

Depreciation expense for the three months ended June 30, 2019 and 2018 was $0.5 million and $0.2 million, respectively. Depreciation expense for the six months ended June 30, 2019 and 2018 was $0.9 million and $0.5 million, respectively.

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

Accrued Expenses

Accrued expenses consist of the following:

	June 30, 2019	December 31, 2018
	(in thousands)	
Development costs	$ 28,498	$ 21,216
Employee-related expenses	15,585	19,638
Professional services	14,299	10,903
Other accrued expenses	530	237
	$ 58,912	$ 51,994

5. Leases, Commitments and Contingencies

Operating Leases

The Company has leases for office space, vehicles, and certain equipment. All of the leases recorded on the balance sheet are operating leases. The Company's leases have remaining lease terms ranging from less than one year to approximately six years. Some of the leases include options to extend the leases for up to five years and 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.

The Company leases office space in two multi-tenant buildings in Cambridge, Massachusetts, consisting, as of June 30, 2019, of 63,017 square feet in the first building under an operating lease that will expire on August 31, 2024 and 19,805 square feet in the second building under an operating lease that will expire on August 31, 2024.

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

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

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

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

In March 2019, the Company entered into the Eighth Amendment to the lease for office space in the first building and thereby increased the amount of square feet of office space from 58,442 square feet to 63,017 square feet. The increase of 4,575 square feet began on June 1, 2019. The term for this additional space will expire on August 31, 2024.

The following table summarizes the presentation in the Company's condensed consolidated balance sheets of operating leases:

(In thousands)	Balance sheet location	As of June 30, 2019
Assets		
Right of use operating asset	Right of use operating asset	$ 37,224
Liabilities		
Current operating lease liabilities	Other current liabilities	7,393
Long-term operating lease liabilities	Long-term lease operating liability, net of current portion	33,309
Total operating lease liabilities		$ 40,702

The following table summarizes the effect of lease costs in the Company's condensed consolidated statements of operations and comprehensive loss:

(In thousands)	Three Months Ended June 30, 2019	Six Months Ended June 30, 2019
Operating lease cost	$ 2,436	$ 4,880

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 in profit or loss 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. For the three and six months ended June 30, 2019, the Company recorded $0.1 million and $0.3 million of expense for its short-term leases, respectively.

The minimum lease payments are expected to be as follows:

Years Ending December 31,	(in thousands)
2019 (remaining six months)	$ 5,080
2020	10,244
2021	9,972
2022	8,898
2023	9,105
Thereafter	5,560
Total lease payments	48,859
Less imputed interest	(8,157)
Present value of operating lease liabilities	$ 40,702

Under the prior lease guidance, future minimum lease payments under non-cancelable operating leases were as follows at December 31, 2018:

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

The weighted average remaining lease term and weighted average discount rate of the Company's operating leases are as follows:

	As of June 30, 2019
Weighted average remaining lease term in years	4.86
Weighted average discount rate	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.

Supplemental disclosure of cash flow information related to the Company's operating leases included in cash flows used by operating activities in the condensed consolidated statements of cash flows is as follows:

(In thousands)	Three Months Ended June 30, 2019	Six Months Ended June 30, 2019
Cash paid for amounts included in the measurement of lease liabilities	$ 2,513	$ 4,867
Right-of-use assets obtained in exchange for lease obligations:		
Operating leases	$ 872	$ 872

During the three and six months ended June 30, 2019, other than the initial adoption of the lease standard that required right of use assets and lease liabilities to be recorded, one right of use asset was recorded arising from new lease liabilities. In March 2019, the Company entered into the Eighth Amendment to the lease for office space in the first building and thereby increased the amount of square feet of office space from 58,442 square feet to 63,017 square feet. The increase of 4,575 square feet began on June 1, 2019. The term for this additional space will expire on August 31, 2024.

License Agreements

CyDex License Agreement

In September 2015, the Company and CyDex amended and restated their existing commercial license agreement. Under the terms of the commercial license agreement as amended and restated, CyDex has granted to the Company an exclusive license to CyDex's Captisol drug formulation technology and related intellectual property for the manufacture of pharmaceutical products incorporating brexanolone and the Company's compound known as SAGE-689, and the development and commercialization of the resulting products in the treatment, prevention or diagnosis of any disease or symptom in humans or animals other than (i) the ocular treatment of any disease or condition with a formulation, including a hormone; (ii) topical ocular treatment of inflammatory conditions; (iii) treatment and prophylaxis of fungal infections in humans; and (iv) any ocular treatment for retinal degeneration. The Company is required to pay a royalty to CyDex on sales of brexanolone and will be required to pay a royalty on sales of SAGE-689, if successfully developed in the future. Royalty rates are in the low single digits based on levels of net sales. As of June 30, 2019, the Company has paid to CyDex $1.0 million for licensing fees, which was recorded as research and development expense.

The Company is obligated to make milestone payments under the amended and restated license agreement with CyDex based on the achievement of clinical development and regulatory milestones in the amount of up to $0.8 million in clinical milestones and up to $3.8 million in regulatory milestones for each of the first two fields with respect to brexanolone; up to $1.3 million in clinical milestones and up to $8.5 million in regulatory milestones for each of the third and fourth fields with respect to brexanolone; and up to $0.8 million in clinical milestones and up to $1.8 million in regulatory milestones for one field with respect to SAGE-689. As of June 30, 2019, the Company has recorded research and development expense and made cash payments of $2.3 million related to these clinical development and regulatory milestones; and has recorded an intangible asset and made a cash payment of $3.0 million.

For the three months ended June 30, 2019, 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 under the license agreement with CyDex. For the six months ended June 30, 2019, the Company recorded an intangible asset and made a cash payment of $3.0 million related to a regulatory milestone for the brexanolone program under the license agreement with CyDex. For the three and six months ended June 30, 2018, the Company recorded research and development expense and made cash payments of $0.8 million related to regulatory milestones for the brexanolone program 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 under which the Company was granted a non-exclusive license to certain clinical data and clinical material related to brexanolone for use in the development and commercialization of biopharmaceutical products in the licensed field, including status epilepticus and postpartum depression. In May 2014, the license agreement was amended to add the treatment of essential tremor to the licensed field of use, materials and milestone fee provisions of the agreement. As of December 31, 2015, the Company paid to The Regents of the University of California clinical development milestones of $0.1 million. 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. The license will terminate on the earlier to occur of (i) 27 years after the effective date or (ii) 15 years after the last-derived product is first commercially sold.

In June 2015, the Company entered into an exclusive license agreement with The Regents of the University of California whereby the Company was granted an exclusive license to certain patent rights related to the use of allopregnanolone to treat various diseases. In exchange for such license, the Company paid an upfront payment of $50,000 and will make payments of $15,000 for annual maintenance fees until the calendar year following the first sale, if any, of a licensed product. The Company is obligated to make milestone payments following the achievement of specified regulatory and sales milestones of up to $0.7 million and $2.0 million in the aggregate, respectively. Following the first sale of a licensed product, the Company is required to pay royalties at a low single digit percentage of net sales of licensed products, subject to specified minimum annual royalty amounts. Unless terminated by operation of law or by acts of the parties under the terms of the agreement, the license agreement will terminate when the last-to-expire patents or last-to-be abandoned patent applications expire, whichever is later. As of June 30, 2019, 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 three months ended June 30, 2019, the Company did not record any expense or make any milestone payments under either license agreement with The Regents of the University of California. For the six months ended June 30, 2019, the Company recorded an intangible asset and made a cash payment of $0.5 million related to a regulatory milestone under the license agreements with The Regents of the University of California. For the three and six months ended June 30, 2018, the Company recorded research and development expense and made cash payments of $0.2 million related to regulatory milestones under the license agreements with The Regents of the University of California.

Washington University License Agreement

In November 2013, the Company entered into a license agreement with Washington University whereby the Company was granted exclusive, worldwide rights to develop and commercialize a novel set of neuroactive steroids developed by Washington University. In exchange for development and commercialization rights, the Company paid an upfront, non-refundable payment of $50,000 and is required to pay an annual license maintenance fee of $15,000 on each subsequent anniversary date, until the first Phase 2 clinical trial for a licensed product is initiated. The Company is obligated to make milestone payments to Washington University based on achievement of clinical development and regulatory milestones of up to $0.7 million and $0.5 million, respectively. Additionally, the Company fulfilled its obligation to issue to Washington University 47,619 shares of common stock on December 13, 2013. The fair value of these shares of $0.1 million was recorded as research and development expense in 2013. As of June 30, 2019, the Company has recorded research and development expense and made a cash payment of $50,000 related to these clinical and development milestones.

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

For the three and six months ended June 30, 2019 and 2018, the Company did not record any expense or make any milestone payments under the license agreement with Washington University.

Consulting Agreement

In January 2014, the Company entered into a consulting agreement with a then non-employee advisor whereby the Company is obligated to make cash payments of up to $2.0 million and to issue up to 126,984 shares of common stock upon attainment of certain clinical development and regulatory milestones. As of June 30, 2019, the Company recorded research and development expense of $1.8 million, comprised of $0.5 million in cash and $1.3 million related to the issuance of 39,681 shares of the Company's common stock, related to the achievement of these milestones.

For the three and six months ended June 30, 2019 and 2018, the Company did not record any expense or make any milestone payments under the consulting agreement with the non-employee advisor.

6. Collaboration Agreement

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

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

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

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

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

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

7. Sale of Equity Securities

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

On February 27, 2019, the Company completed the sale of 3,833,334 shares of its common stock in an underwritten public offering at a price to the public of $150.00 per share, resulting in net proceeds of $560.9 million after deducting commissions and underwriting discounts and offering costs paid by the Company.

8. Stock-Based Compensation

Restricted Stock Units

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

During the three months ended March 31, 2018, the Company granted 33,600 performance restricted stock units to certain employees of the Company. The milestones for these grants were not met, and accordingly, these grants were cancelled.

During the three months ended June 30, 2018, the Company granted 37,800 performance restricted stock units to certain employees of the Company. These performance restricted stock units will vest upon the achievement of a certain commercial milestone.

During the three and six months ended June 30, 2019, the Company granted 16,345 and 370,456, performance restricted stock units, respectively, to employees of the Company. These performance restricted stock units will vest upon the achievement of a certain clinical and regulatory development milestones related to product candidates and a commercial milestone.

The fair value of restricted stock units that vested during the six months ended June 30, 2019 and 2018 was $2.0 million and $2.6 million, respectively. No restricted stock units vested during the three months ended June 30, 2019 and 2018.

The table below summarizes activity relating to restricted stock units:

	Shares
Outstanding as of December 31, 2018	82,700
Granted	370,456
Vested	(13,250)
Forfeited	(43,240)
Outstanding as of June 30, 2019	396,666

Stock Option Plans

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

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

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

As of June 30, 2019, the total number of shares reserved under all equity plans was 11,045,846, and 2,781,281 shares were available for future issuance under such plans.

During the three and six months ended June 30, 2018, the Company granted 200,250 and 524,003 options, respectively, to employees to purchase shares of common stock that contain performance-based vesting criteria, primarily related to the achievement of certain clinical and regulatory development milestones related to product candidates and a commercial milestone. Recognition of stock-based compensation expense associated with these performance-based stock options commences when the performance condition is considered probable of achievement, using management’s best estimates, which consider the inherent risk and uncertainty regarding the future outcomes of the milestones.

During the six months ended June 30, 2019, the Company granted no options to employees to purchase shares of common stock that contain performance-based vesting criteria.

During the three months ended March 31, 2019, the achievement of one un-met commercial milestone that is the criteria for vesting of performance-based stock options was considered probable, and therefore $14.2 million of stock-based compensation expense was recognized related to these awards for the three months ended March 31, 2019. Stock options with this milestone were granted during the years ended December 31, 2018 and 2017. During the three months ended June 30, 2019, this commercial milestone was achieved. This milestone represents 20% and 33% of the performance-based option grants that were made during the years ended December 31, 2018 and 2017, respectively. During the three months ended June 30, 2019, the Company recognized stock-based compensation expense related to this milestone of $2.1 million. During the six months ended June 30, 2019, the Company recognized stock-based compensation expense related to this milestone of $16.3 million.

As of June 30, 2018, for grants that were outstanding, the achievement of the milestones that had not been met that are the criteria for vesting of performance-based stock options was considered not probable, and therefore no expense had been recognized related to these awards for the six months ended June 30, 2018.

As of June 30, 2019, for grants that were outstanding, the achievement of the milestones that had not been met that are the criteria for vesting of performance-based stock options was considered not probable, and therefore no expense had been recognized related to these awards for the three months ended June 30, 2019.

During the three months ended June 30, 2018, a performance milestone was achieved under a stock option granted to a consultant. The milestone was related to the consummation of a licensing or corporate partnering arrangement. During the three months ended June 30, 2018, the Company recognized stock-based compensation expense related to this milestone of $6.9 million.

Stock-based compensation expense for stock options, restricted stock units and the employee stock purchase plan recognized during the three and six months ended June 30, 2019 and 2018 was as follows:

	Three Months Ended June 30, 2019	Three Months Ended June 30, 2018	Six Months Ended June 30, 2019	Six Months Ended June 30, 2018
	(in thousands)			
Research and development	$ 13,672	$ 12,095	$ 34,417	$ 20,994
Selling, general and administrative	21,095	16,933	44,466	23,851
	$ 34,767	$ 29,028	$ 78,883	$ 44,845

Stock-based compensation expense by award type recognized during the three and six months ended June 30, 2019 and 2018 was as follows:

	Three Months Ended June 30, 2019	Three Months Ended June 30, 2018	Six Months Ended June 30, 2019	Six Months Ended June 30, 2018
	(in thousands)			
Stock options	$ 34,280	$ 28,627	$ 77,844	$ 44,007
Restricted stock units	—	155	58	324
Employee stock purchase plan	487	246	981	514
	$ 34,767	$ 29,028	$ 78,883	$ 44,845

The weighted average grant date fair value per share of stock options granted under the Company's stock option plans during the six months ended June 30, 2019 and 2018 was $99.11 and $114.72, respectively.

The table below summarizes activity related to stock options:

	Shares	Weighted Average Exercise Price	Weighted Average Remaining Life (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2018	7,530,767	$ 93.22	8.03	$ 227,447
Granted	1,355,931	—		
Exercised	(745,558)	—		
Forfeited	(281,850)	—		
Outstanding as of June 30, 2019	7,859,290	$ 107.81	7.98	$ 600,965
Exercisable as of June 30, 2019	3,321,049	$ 70.02	6.89	$ 378,713

At June 30, 2019, the Company had unrecognized stock-based compensation expense related to its unvested service-based stock option awards of $310.7 million, which is expected to be recognized over the remaining weighted average vesting period of 2.74 years.

The intrinsic value of stock options exercised during the six months ended June 30, 2019 and 2018 was $87.4 million and $64.4 million, respectively.

At June 30, 2019, 505,131 performance-based stock options were both outstanding and unvested, and the total unrecognized stock-based compensation expense related to those awards was $35.2 million.

9. Net Loss Per Share

Basic and diluted net loss per share was calculated as follows for the three and six months ended June 30, 2019 and 2018:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Basic net loss per share:				
Numerator:				
Net loss (in thousands)	$ (168,221)	$ (16,978)	$ (331,627)	$ (91,576)
Denominator:				
Weighted average common stock outstanding - basic	51,257,640	46,541,716	49,882,377	45,439,666
Dilutive effect of shares of common stock equivalents resulting from common stock options and restricted stock units	—	—	—	—
Weighted average common stock outstanding - diluted	51,257,640	46,541,716	49,882,377	45,439,666
Net loss per share—basic and diluted	$ (3.28)	$ (0.36)	$ (6.65)	$ (2.02)

The following common stock equivalents outstanding as of June 30, 2019 and 2018 were excluded from the calculation of diluted net loss per share for the periods presented because including them would have been anti-dilutive:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Stock options	7,362,768	6,207,172	7,362,768	6,207,172
Restricted stock units	—	13,950	—	13,950
Employee stock purchase plan	39,006	8,004	39,006	8,004
	7,401,774	6,229,126	7,401,774	6,229,126

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.

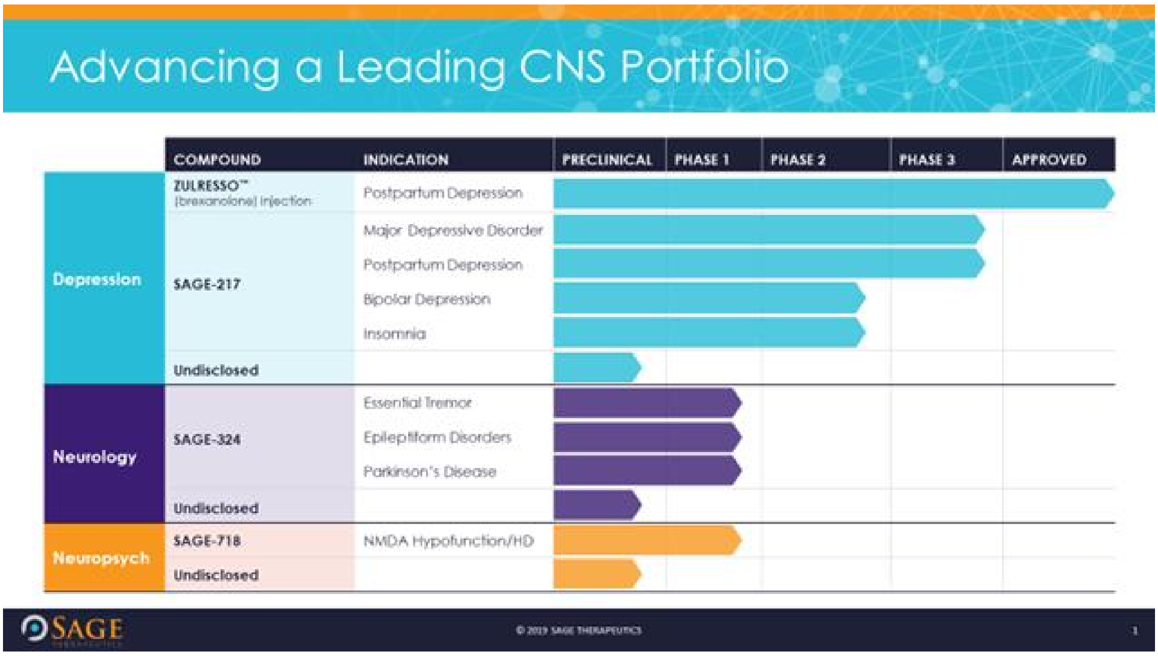
Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our unaudited condensed consolidated financial statements and related notes appearing elsewhere in this Quarterly Report on Form 10-Q, or Quarterly Report, and the audited financial statements and related notes contained in our Annual Report on Form 10-K for the year ended December 31, 2018, 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 Quarterly Report. We discuss risks and other factors that we believe could cause or contribute to these potential differences elsewhere in this report, including under Part II, Item 1A. "Risk Factors" and under "Cautionary Note Regarding Forward-Looking Statements" in this Quarterly 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 Quarterly 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, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the Securities and Exchange Commission, or SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

Overview

We are a biopharmaceutical company committed to developing and commercializing novel medicines with the potential to transform the lives of people with debilitating disorders of the brain. Our lead product, ZULRESSO™ (brexanolone) injection, was approved by the U.S. Food and Drug Administration, or FDA, in March 2019 for the treatment of postpartum depression, or PPD, in adults, and was made commercially available in the U.S. beginning on June 24, 2019, after 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. We have a portfolio of other product candidates with a current focus on modulating two critical CNS receptor systems, GABA and NMDA. The GABA receptor family, which is recognized as the major inhibitory neurotransmitter in the CNS, mediates downstream neurologic and bodily function via activation of GABAA receptors. The NMDA-type receptors of the glutamate receptor system are a major excitatory receptor system in the CNS. Dysfunction in these systems is implicated in a broad range of CNS disorders. We are targeting CNS indications where patient populations are easily identified, clinical endpoints are well-defined, and development pathways are feasible.

The following table summarizes the status of our product and product candidate portfolio as of the filing date of this Quarterly Report.



Our lead product, ZULRESSO™ (brexanolone) injection, is a proprietary intravenous, or IV, formulation of brexanolone. Brexanolone is chemically identical to allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of GABAA receptors. In March 2019, the FDA approved ZULRESSO for the treatment of PPD in adults. We launched ZULRESSO commercially in the U.S. beginning on June 24, 2019, after completion of controlled substance scheduling of brexanolone by the 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. PPD is a common biological complication of childbirth, and is characterized by significant depressive symptoms that typically commence during the third trimester of pregnancy or in the months following childbirth. 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 to allow us to compile additional information to further our understanding of the risk of 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, we expect use of ZULRESSO will, at least initially, be focused primarily on women with severe PPD. We estimate that about 20 to 30% of women diagnosed with PPD fall into this category.

We have received PRIority MEdicines, or PRIME, designation from the European Medicines Agency, or EMA, in the European Union, or EU, for our proprietary formulation of brexanolone as a potential treatment for PPD. The EMA has requested that we conduct an additional clinical trial evaluating brexanolone in the treatment of PPD to support submission of a potential marketing authorization application, or MAA, seeking approval of brexanolone in such indication. We will continue to evaluate the EMA's request in light of our overall portfolio and program priorities as well as the potential timing of development in the EU of SAGE-217, our next most advanced product candidate.

Our next most advanced product candidate is SAGE-217, an oral compound that is currently in Phase 3 clinical development for PPD and major depressive disorder, or MDD. SAGE-217 is a novel neuroactive steroid that, like brexanolone, is a positive allosteric modulator of GABAA receptors, targeting both synaptic and extrasynaptic GABAA receptors. The FDA has granted Breakthrough Therapy designation and Fast Track designation to SAGE-217 in the treatment of MDD. We have completed two positive placebo-controlled pivotal clinical trials with SAGE-217, one in MDD completed in 2017 and one in PPD for which top-line results were announced in January 2019. The ongoing Phase 3 clinical program for SAGE-217 in MDD is comprised of:

- a placebo-controlled Phase 3 clinical trial in patients with MDD, known as the Mountain Study, in which we are studying two weeks of treatment with SAGE-217 followed by four weeks of follow-up, with an open-label extension to continue to follow patients for up to six months;
- an ongoing open-label retreatment study, known as the Shoreline Study, evaluating initial treatment with SAGE-217, treatment-free intervals, and as needed retreatment, in patients with MDD in which patients will be followed for up to a year after treatment; and
- a placebo-controlled trial to evaluate fixed interval SAGE-217 monotherapy (treatment without traditional antidepressants) for up to a year, known as the Redwood Study; and

We are also conducting a placebo-controlled polysomnography Phase 3 clinical trial of SAGE-217 in patients with MDD who have co-morbid insomnia, known as the Rainforest Study. We expect to report top-line results from the Mountain Study in the fourth quarter of 2019 or the first quarter of 2020. We expect to report top-line results from the Shoreline Study and the Rainforest Study in 2020. We expect to initiate the Redwood Study in the third quarter of 2019.

We also plan to explore SAGE-217 in other indications. Based on analysis of subpopulations of patients from our completed placebo-controlled clinical trials of SAGE-217 in MDD and PPD who had ongoing symptoms of depression at baseline despite receiving standard anti-depressant pharmacotherapy, we plan to initiate clinical trials of SAGE-217 in the treatment of treatment resistant depression, or TRD. We also plan to continue to evaluate the potential for development of SAGE-217 in generalized anxiety disorder and bipolar depression. In July 2019, we reported positive top-line results from a small open-label clinical trial of SAGE-217 in patients with bipolar depression.

In addition to SAGE-217, we have a portfolio of other novel compounds that target GABAA receptors. SAGE-324 is a novel GABAA receptor positive allosteric modulator with preclinical pharmacokinetic and pharmacodynamic properties that suggest suitability for chronic oral dosing. We plan to develop SAGE-324 for a number of neurological conditions, including essential tremor, epileptiform disorders and Parkinson's disease. Results from our Phase 1 clinical program demonstrated that the profile of SAGE-324 includes good oral bioavailability and a pharmacokinetic profile consistent with once-daily dosing. We have also studied SAGE-324 in a Phase 1 single dose, open-label trial involving a small number of patients with essential tremor. Based on the results of the Phase 1 clinical program, including the positive signal observed in the small cohort of patients with essential tremor, and our other work in this area to date, we plan to initiate a Phase 2 clinical trial evaluating SAGE-324 in the treatment of essential tremor in the second half of 2019. Our portfolio of novel GABAA receptor positive allosteric modulators also includes SAGE-689, with which we have conducted non-clinical studies to date, and other compounds at earlier stages of development with a focus on both acute and chronic CNS disorders.

Our second area of focus is the development of novel compounds that target the NMDA receptor. The first product candidate selected for development from this program is SAGE-718, an oxysterol-based positive allosteric modulator of the NMDA receptor, which we are exploring in certain cognition-related disorders impacted by NMDA receptor dysfunction. Examples of indications involving NMDA receptor dysfunction include certain types, aspects or subpopulations of a number of diseases such as depression, Huntington's disease, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, and neuropathic pain. We have completed a Phase 1 single ascending dose trial and multiple ascending dose trials of SAGE-718. We have also completed a suite of Phase 1 clinical trials in healthy volunteers designed to demonstrate CNS-target engagement using a low-dose ketamine challenge paradigm. SAGE-718 demonstrated a long half-life consistent with once-daily dosing in Phase 1 clinical trials. Results of an integrated analysis of the target engagement studies in healthy volunteers demonstrated that SAGE-718 had effects on electrophysiological, functional neuroimaging, and cognitive measures consistent with CNS activity. In addition, healthy volunteers dosed with

SAGE-718 in the trials exhibited superior performance on tests of working memory and complex problem solving than the placebo-group. A Phase 1 clinical trial to evaluate the safety, tolerability and pharmacokinetics of SAGE-718 in a small number of patients with early manifest Huntington's disease is ongoing. We expect to report top-line results from this trial in the second half of 2019. Based on the results we have generated to date in the SAGE-718 Phase 1 clinical program, we plan to evaluate SAGE-718 in a Phase 2 development program in certain neurodegenerative disorders and other conditions where executive function is impaired.

We expect to continue our work on allosteric modulation of the GABAA and NMDA receptor systems in the brain. The GABAA 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 continue to evaluate business development opportunities in potential new areas of interest.

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 on June 24, 2019. Prior to the second quarter of 2019, all of our revenue had been derived from a strategic collaboration we entered into in the second quarter of 2018 with Shionogi & Co., Ltd., or Shionogi, for the clinical development and commercialization of SAGE-217 in Japan, Taiwan and South Korea. The initial list price for ZULRESSO in the U.S. is $7,450 per vial, which we estimate will result in a projected average course of therapy cost of $34,000 per patient before discounts based on an assumption of an average of 4.5 vials used per patient. The actual number of vials used and resulting cost of therapy per patient before discounts will vary by patient and by healthcare setting. Given the timing of U.S. launch of ZULRESSO and the time required for healthcare settings to become REMS-certified, achieve formulary approvals, establish protocols for administering ZULRESSO and secure satisfactory reimbursement which may take six to nine months or more, depending on the site, we do not expect to start to see revenue momentum from sales of ZULRESSO to build, if such momentum is achieved, until the fourth quarter of 2019 into 2020.

We have incurred net losses in each year since our inception, and we have an accumulated deficit of $1.3 billion as of June 30, 2019. Our net losses were $331.6 million for the six months ended June 30, 2019 and $372.9 million for the year ended December 31, 2018. 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 substantially in connection with our ongoing activities, as we:

- continue our commercialization efforts with respect to ZULRESSO in the treatment of PPD in the U.S.;
- fulfill our post-approval commitments related to ZULRESSO;
- continue to advance clinical development of SAGE-217, including the ongoing Phase 3 clinical program in MDD and initiation of development in TRD;
- continue to advance clinical development of SAGE-324 with an initial focus on development in essential tremor, certain epileptiform disorders, and potentially other neurological conditions;
- continue to advance clinical development of SAGE-718 with an initial focus on development in indications involving NMDA receptor hypofunction;
- advance one or more non-clinical stage compounds into Phase 1 clinical development;
- continue our research and development efforts to evaluate the potential for our existing product candidates in the treatment of additional indications or in new formulations, and to identify new drug candidates in the treatment of CNS disorders;
- determine the potential development and regulatory pathway for SAGE-217 in the EU;
- seek regulatory approvals for any product candidates that successfully complete clinical development;

- continue to manufacture supplies of SAGE-217 for ongoing late stage clinical trials; refine the formulation and improve the manufacturing process for our other product candidates; and manufacture clinical supplies as development progresses;
- add personnel, including personnel to support our product development and ongoing and future commercialization efforts, and incur increases in stock-based compensation expense related to existing and new personnel with respect to both service-based and performance-based awards;
- evaluate market opportunities for our products and product candidates in markets outside the U.S.;
- evaluate business development opportunities in potential new areas of interest;
- add operational, financial and management information systems; and
- maintain, leverage and expand our intellectual property portfolio.

Until such time that we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of revenue, equity or debt financings or other sources, which may include collaborations with third parties. We may not be successful in our commercialization of ZULRESSO, and may not generate revenues at the levels we expect. We may never successfully complete development of any of our current or future product candidates, 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 as and when needed would have a negative impact on our financial condition and on our ability to pursue our business strategy. Arrangements with collaborators or others may require us to relinquish rights to certain of our technologies or product candidates. We will need to generate significant revenue to achieve profitability, and we may never do so.

We expect that our existing cash, cash equivalents and marketable securities as of June 30, 2019 will enable us to fund our operating expenses and capital expenditure requirements, based on our current operating plan, at least the next 12 months from the filing date of this Quarterly Report. 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 launch of our first product, ZULRESSO, which commenced on June 24, 2019. Prior to the second quarter of 2019, all of our revenue had been derived from a strategic collaboration we entered into in the second quarter of 2018 with Shionogi. All of our revenue from sales of ZULRESSO in the second quarter of 2019 was attributable to channel stocking of ZULRESSO by distributors upon launch of the product. No patients had been administered ZULRESSO using commercial product as of the end of the second quarter of 2019. Given the timing of U.S. launch of ZULRESSO, and the time required for healthcare settings to become REMS-certified, achieve formulary approvals, establish protocols for administering ZULRESSO and secure satisfactory reimbursement which may take six to nine months or more, depending on the site, we do not expect to start to see revenue momentum from sales of ZULRESSO to build, if such momentum is achieved, until the fourth quarter of 2019 into 2020. We expect that, even if we start to see revenue momentum in the fourth quarter of 2019, revenues are likely to fluctuate quarter to quarter. We will not generate revenue from other products unless and until we 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 product candidates. We expect that revenue, if any, we generate under collaboration agreements will fluctuate from quarter to quarter as a result of the timing and amount of license fees, research and development services and related reimbursements, payments for clinical materials or manufacturing services, and milestone and other payments.

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 revenues and amortization of intangible assets associated with ZULRESSO.

Operating Expenses

Our operating expenses since inception have consisted 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 clinical trials and developing external manufacturing capabilities;
- costs of outside consultants engaged in research and development activities, including their fees, stock-based compensation and travel expenses;
- other expenses related to our non-clinical studies and clinical trials and expenses related to our regulatory activities; and
- payments made under our third-party license agreements.

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

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

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

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 facilities and other related expenses, including rent, depreciation, maintenance of facilities, insurance and supplies; professional fees for expenses incurred under agreements with third parties relating to the commercialization of ZULRESSO; and for public relations, audit, tax and legal services, including legal expenses to pursue patent protection of our intellectual property.

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

Results of Operations

Comparison of the Three Months Ended June 30, 2019 and 2018

The following table summarizes our results of operations for the three months ended June 30, 2019 and 2018:

	Three Months Ended June 30,		Increase
	2019	2018	(Decrease)
	(in thousands)		
Product revenue, net	$ 519	$ —	$ 519
Collaboration revenue	354	90,000	(89,646)
Total revenue	873	90,000	(89,127)
Operating costs and expenses:			
Cost of goods sold	44	—	44
Research and development	89,059	68,980	20,079
Selling, general and administrative	88,227	43,167	45,060
Total operating costs and expenses	177,330	112,147	65,183
Loss from operations	(176,457)	(22,147)	(154,310)
Interest income, net	8,220	5,137	3,083
Other income, net	16	32	(16)
Net loss	$ (168,221)	$ (16,978)	$ (151,243)

Product revenue, net

We began to record net product revenues in the second quarter of 2019 following the approval of ZULRESSO by the FDA on March 19, 2019 and its subsequent commercial launch in the United States in June 2019. During the three months ended June 30, 2019, we recognized $0.5 million of net product revenues related to sales of ZULRESSO. All of our revenue from sales of ZULRESSO in the second quarter of 2019 was attributable to channel stocking of ZULRESSO by distributors upon launch of the product. No patients had been administered ZULRESSO using commercial product as of the end of the second quarter of 2019. Sales allowances and accruals consisted of patient financial assistance, distribution fees, discounts, and chargebacks.

Collaboration revenue

For the three months ended June 30, 2019, we recognized $0.4 million in collaboration revenue from our agreement with Shionogi related to the supply of SAGE-217 drug product for clinical development. For further discussion regarding our collaboration agreement with Shionogi and the accounting for revenue from collaboration agreements, refer to Note 6, Collaboration Agreement and Note 2, Summary of Significant Accounting Policies in the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report.

Effective June 12, 2018, we entered into a strategic collaboration with Shionogi for the clinical development and commercialization of SAGE-217 for the treatment of MDD and other potential indications in Japan, Taiwan and South Korea. Under the terms of the agreement, Shionogi will be responsible for all clinical development, regulatory filings and commercialization of SAGE-217 for MDD, and potentially other indications, in Japan, Taiwan and South Korea. Shionogi was required to make an upfront payment to us upon execution of the agreement of $90.0 million, and it was recorded as collaboration revenue in the three months ended June 30, 2018.

Cost of goods sold

Cost of goods sold of $44,000 for the three months ended June 30, 2019 is related to royalties on net sales payable to CyDex and The Regents of the University of California under license agreements (see Note 5, Leases, Commitments and Contingencies in the Notes to Condensed Consolidated Financial Statements included in Part I of this Quarterly Report), labeling and packaging costs incurred after FDA approval, and certain distribution costs. Prior to receiving regulatory approval for ZULRESSO on March 19, 2019, we manufactured ZULRESSO inventory to be sold upon commercialization and recorded all costs incurred 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 three months ended June 30, 2019. We expect our cost of goods sold of ZULRESSO to increase as a percentage of net sales in future periods as we produce and then sell inventory that reflects the full cost of manufacturing.

Research and development expenses

	Three Months Ended June 30,		Increase
	2019	2018	(Decrease)
		(in thousands)	
brexanolone (SAGE-547)	$ 2,350	$ 9,643	$ (7,293)
SAGE-217	37,450	15,600	21,850
SAGE-324	4,367	1,242	3,125
SAGE-718	1,453	2,781	(1,328)
Other research and development programs	10,248	8,009	2,239
Unallocated expenses	19,519	19,610	(91)
Stock-based compensation	13,672	12,095	1,577
Total research and development expenses	$ 89,059	$ 68,980	$ 20,079

Research and development expenses for the three months ended June 30, 2019 were $89.1 million, compared to $69.0 million for the three months ended June 30, 2018. The increase of $20.1 million was primarily due to the following:

- a decrease of $7.3 million in expenses related to our brexanolone program, due to the completion of the Phase 3 clinical trials in PPD;
- an increase of $21.9 million in expenses related to conduct of our Phase 3 clinical trials of SAGE-217 in MDD and supporting supply chain activities;
- an increase of $3.1 million in expenses related to conduct of our Phase 1 clinical trials of SAGE-324;
- a decrease of $1.3 million in expenses related to conduct of our Phase 1 clinical trials of SAGE-718;
- an increase of $2.2 million in expenses related to research and development programs and discovery efforts focused on identifying new clinical candidates and additional indications of interest, and on our back-up programs; and
- an increase of $1.6 million in non-cash stock-based compensation expense, due to the hiring of additional full-time employees to support the growth of our operations and the increase in the fair market value of our common stock. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $1.0 million for the three months ended June 30, 2019. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the three months ended June 30, 2018.

Selling, general and administrative expenses

	Three Months Ended June 30, 2019	Three Months Ended June 30, 2018	Increase (Decrease)
	(in thousands)		
Personnel-related	$ 31,993	$ 11,432	$ 20,561
Stock-based compensation	21,095	16,933	4,162
Professional fees	20,670	10,953	9,717
Other	14,469	3,849	10,620
Total selling, general and administrative expenses	$ 88,227	$ 43,167	$ 45,060

Selling, general and administrative expenses for the three months ended June 30, 2019 and 2018 were $88.2 million and $43.2 million, respectively. The increase of $45.1 million was primarily due to the following:

- an increase of $20.6 million in personnel-related costs in connection with the hiring of additional full-time employees to support the growth of our operations and commercial-related activities;
- an increase of $4.2 million in non-cash stock-based compensation expense, due to the hiring of additional full-time employees to support the growth of our operations and the increase in the fair market value of our common stock. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $1.1 million for the three months ended June 30, 2019. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $6.9 million during the three months ended June 30, 2018 for a milestone related to the consummation of a licensing or corporate partnering arrangement;
- an increase of $9.7 million in professional fees associated with expanding operations, primarily for costs related to preparations for the launch of ZULRESSO in the U.S., which commenced on June 24, 2019; and
- an increase of $10.6 million in other expenses due to increased costs associated with facilities, mainly due to the increase in the amount of rented square feet of office space to accommodate our increased number of employees, along with other corporate infrastructure and office-related costs, such as information technology costs.

Interest income, net and Other expense, net

Interest income, net, and other expense, net, for the three months ended June 30, 2019 and 2018 were $8.2 million and $5.2 million, respectively. The primary reason for the increase was an increase in the balance of marketable securities.

Comparison of the Six Months Ended June 30, 2019 and 2018

The following table summarizes our results of operations for the six months ended June 30, 2019 and 2018:

	Six Months Ended June 30, 2019	Six Months Ended June 30, 2018	Increase (Decrease)
	(in thousands)		
Product revenue, net	$ 519	$ —	$ 519
Collaboration revenue	819	90,000	(89,181)
Total revenue	1,338	90,000	(88,662)
Operating costs and expenses:			
Cost of goods sold	44	—	44
Research and development	175,457	118,250	57,207
Selling, general and administrative	172,146	72,016	100,130
Total operating costs and expenses	347,647	190,266	157,381
Loss from operations	(346,309)	(100,266)	(246,043)
Interest income, net	14,662	8,666	5,996
Other income, net	20	24	(4)
Net loss	$ (331,627)	$ (91,576)	$ (240,051)

Product revenue, net

We began to record net product revenues in the second quarter of 2019 following the approval of ZULRESSO by the FDA on March 19, 2019 and its subsequent commercial launch in the United States in June 2019. During the six months ended June 30, 2019, we recognized $0.5 million of net product revenues related to sales of ZULRESSO. All of our revenue from sales of ZULRESSO in the second quarter of 2019 was attributable to channel stocking of ZULRESSO by distributors upon launch of the product. No patients had been administered ZULRESSO using commercial product as of the end of the second quarter of 2019. Sales allowances and accruals consisted of patient financial assistance, distribution fees, discounts, and chargebacks.

Collaboration revenue

For the six months ended June 30, 2019, we recognized $0.8 million in collaboration revenue from our agreement with Shionogi related to the supply of SAGE-217 drug product for clinical development. For further discussion regarding our collaboration agreement with Shionogi and the accounting for revenue from collaboration agreements, refer to Note 6, Collaboration Agreement and Note 2, Summary of Significant Accounting Policies in the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report.

Effective June 12, 2018, we entered into a strategic collaboration with Shionogi for the clinical development and commercialization of SAGE-217 for the treatment of MDD and other potential indications in Japan, Taiwan and South Korea. Under the terms of the agreement, Shionogi will be responsible for all clinical development, regulatory filings and commercialization of SAGE-217 for MDD, and potentially other indications, in Japan, Taiwan and South Korea. Shionogi was required to make an upfront payment to us upon execution of the agreement of $90.0 million, and it was recorded as collaboration revenue in the six months ended June 30, 2018.

Cost of goods sold

Cost of goods sold of $44,000 for the six months ended June 30, 2019 is related to royalties on net sales payable to CyDex and The Regents of the University of California related to license agreements (see Note 5, Leases, Commitments and Contingencies in the Notes to Condensed Consolidated Financial Statements included in Part I of this Quarterly Report), labeling and packaging costs incurred after FDA approval, and certain distribution costs. Prior to receiving regulatory approval for ZULRESSO on March 19, 2019, we manufactured ZULRESSO inventory to be sold upon commercialization and recorded all costs incurred 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 six months ended June 30, 2019. We expect our cost of goods sold of ZULRESSO to increase as a percentage of net sales in future periods as we produce and then sell inventory that reflects the full cost of manufacturing.

Research and development expenses

	Six Months Ended June 30, 2019	Six Months Ended June 30, 2018	Increase (Decrease)
	(in thousands)		
brexanolone (SAGE-547)	$ 4,248	$ 18,186	$ (13,938)
SAGE-217	67,679	20,987	46,692
SAGE-324	7,278	2,761	4,517
SAGE-718	6,949	4,217	2,732
Other research and development programs	17,491	14,719	2,772
Unallocated expenses	37,395	36,386	1,009
Stock-based compensation	34,417	20,994	13,423
Total research and development expenses	$ 175,457	$ 118,250	$ 57,207

Research and development expenses for the six months ended June 30, 2019 were $175.5 million, compared to $118.3 million for the six months ended June 30, 2018. The increase of $57.2 million was primarily due to the following:

- a decrease of $13.9 million in expenses related to our brexanolone program, due to the completion of the Phase 3 clinical trials in PPD;
- an increase of $46.7 million in expenses related to conduct of our Phase 3 clinical trials of SAGE-217 in MDD and supporting supply chain activities;
- an increase of $4.5 million in expenses related to conduct of our Phase 1 clinical trials of SAGE-324;
- an increase of $2.7 million in expenses related to conduct of our Phase 1 clinical trials of SAGE-718 and supporting clinical activities;
- an increase of $2.8 million in expenses related to research and development programs and discovery efforts focused on identifying new clinical candidates and additional indications of interest, and on our back-up programs; and
- an increase of $13.4 million in non-cash stock-based compensation expense, due to the hiring of additional full-time employees to support the growth of our operations and the increase in the fair market value of our common stock. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $9.5 million for the six months ended June 30, 2019. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the six months ended June 30, 2018.

Selling, general and administrative expenses

	Six Months Ended June 30, 2019	Six Months Ended June 30, 2018	Increase (Decrease)
	(in thousands)		
Personnel-related	$ 62,164	$ 19,432	$ 42,732
Stock-based compensation	44,466	23,851	20,615
Professional fees	39,045	22,152	16,893
Other	26,471	6,581	19,890
Total selling, general and administrative expenses	$ 172,146	$ 72,016	$ 100,130

Selling, general and administrative expenses for the six months ended June 30, 2019 and 2018 were $172.1 million and $72.0 million, respectively. The increase of $100.1 million was primarily due to the following:

- an increase of $42.7 million in personnel-related costs in connection with the hiring of additional full-time employees to support the growth of our operations and commercial-related activities;
- an increase of $20.6 million in non-cash stock-based compensation expense, due to the hiring of additional full-time employees to support the growth of our operations and the increase in the fair market value of our common stock. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $6.8 million for the six months ended June 30, 2019. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $6.9 million during the six months ended June 30, 2018 for a milestone related to the consummation of a licensing or corporate partnering arrangement;
- an increase of $16.9 million in professional fees associated with expanding operations, primarily for costs related to preparations for the launch of ZULRESSO in the U.S., which commenced on June 24, 2019; and
- an increase of $19.9 million in other expenses due to increased costs associated with facilities, mainly due to the increase in the amount of rented square feet of office space to accommodate our increased number of employees, along with other corporate infrastructure and office-related costs, such as information technology costs.

Interest income, net and Other expense, net

Interest income, net, and other expense, net, for the six months ended June 30, 2019 and 2018 were $14.7 million and $8.7 million, respectively. The primary reason for the increase was an increase in the balance of marketable securities.

Liquidity and Capital Resources

Prior to the second quarter of 2019, we had not generated revenue from product sales. 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 on June 24, 2019. Prior to the second quarter of 2019, all of our revenue had been derived from our collaboration with Shionogi. To date, we have incurred recurring net losses. As of June 30, 2019, we had an accumulated deficit of $1.3 billion. From our inception through June 30, 2019, we received net proceeds of $2.2 billion from the sales of redeemable convertible preferred stock, the issuance of convertible notes and the sales of common stock in our initial public offering in July 2014 and follow-on offerings in April 2015, January 2016, September 2016, November 2017, February 2018 and February 2019.

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

On February 27, 2019, we completed the sale of 3,833,334 shares of our common stock in an underwritten public offering at a price to the public of $150.00 per share, resulting in net proceeds of $560.9 million after deducting commissions and underwriting discounts and offering costs paid by us.

As of June 30, 2019, our primary sources of liquidity were our cash, cash equivalents and marketable securities, which totaled $1.2 billion. We invest our cash in money market funds, U.S. government securities, corporate bonds and commercial paper, with the primary objectives to preserve principal, provide liquidity and maximize income without significantly increasing risk.

The following table summarizes the primary sources and uses of cash for the six months ended June 30, 2019 and 2018:

	Six Months Ended June 30, 2019	Six Months Ended June 30, 2018
Net cash provided by (used in):		
Operating activities	$ (283,278)	$ (78,706)
Investing activities	(333,019)	(550,931)
Financing activities	591,539	649,652
Total	$ (24,758)	$ 20,015

Operating Activities

Cash used in operating activities for the six months ended June 30, 2019 was $283.3 million, compared to $78.7 million for the six months ended June 30, 2018. The increase of $204.6 million was primarily due to the following:

- An increase of $240.1 million in cash used related to our net loss, primarily due to an increase in selling, general and administrative expenses due to increased headcount and other costs to support our expanding operations and increased research and development activities related to our development programs along with increased headcount in related functions;
- Offset by an increase of $31.8 million in non-cash charges, primarily due to an increase in stock-based compensation expense due to increased hiring; and
- A decrease of $3.6 million in cash used in changes in our operating assets and liabilities, primarily due to the growth of the business and the timing of vendor invoicing and payments.

Investing Activities

During the six months ended June 30, 2019 and 2018, net cash used in investing activities was $333.0 million and $550.9 million, respectively. During the six months ended June 30, 2019 and 2018, we purchased marketable securities and had sales and maturities of our marketable securities as part of managing our cash and investments portfolio, including purchases using proceeds received in our underwritten follow-on public offerings during February 2018 and February 2019.

Financing Activities

During the six months ended June 30, 2019 and 2018, net cash provided by financing activities was $591.5 million and $649.7 million, respectively, which primarily consisted of net proceeds from follow-on underwritten public offerings of our common stock, after deducting commissions and underwriting discounts and offering costs.

Operating Capital Requirements

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 on June 24, 2019. Given the timing of the U.S. launch of ZULRESSO and the time required for healthcare settings to become REMS-certified, achieve formulary approvals, establish protocols for administering ZULRESSO and secure satisfactory reimbursement, which may take six to nine months or more, depending on the site, we do not expect to start to see revenue momentum from sales of ZULRESSO build, if such momentum is achieved, until the fourth quarter of 2019 into 2020. We expect that, even if we start to see revenue momentum in the fourth quarter of 2019, revenues are likely to fluctuate quarter to quarter. 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 those product candidates that are successfully developed; prepare for potential future commercialization of product candidates beyond ZULRESSO that are successfully developed and approved; begin to commercialize any such products, if successfully developed and approved; and continue our efforts to identify and develop new product candidates beyond our current portfolio. We also expect to incur additional 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 and any future products that are successfully developed and approved. Accordingly, we anticipate that we will need substantial additional funding in connection with our continuing operations.

Based on our current operating plans, we expect that our existing cash, cash equivalents and marketable securities as of June 30, 2019, will enable us to fund our operating expenses and capital expenditure requirements at least the next 12 months from the filing date of this Quarterly Report. During that time, we expect that our expenses will increase substantially as we:

- continue our commercial activities related to ZULRESSO in the treatment of PPD in the U.S.;
- fulfill our post-approval commitments related to ZULRESSO;
- continue to advance clinical development of SAGE-217, including the ongoing Phase 3 clinical program in MDD;
- continue to advance clinical development of SAGE-324 with an initial focus on development in essential tremor, certain epileptiform disorders, and other neurological conditions;
- continue to advance clinical development of SAGE-718 with an initial focus on development in indications involving NMDA receptor hypofunction;
- advance one or more non-clinical stage compounds into Phase 1 clinical development;
- continue our research and development efforts to evaluate the potential for our product candidates in the treatment of additional indications or in new formulations, and the identification of new drug candidates in the treatment of CNS disorders;
- determine the potential development and regulatory pathway for SAGE-217 in the EU;
- seek regulatory approvals in the U.S. for any product candidates that successfully complete clinical development;
- refine and scale-up the manufacturing process for SAGE-217 for planned late stage clinical trials; continue to improve the manufacturing process for our other product candidates; and manufacture clinical supplies as development progresses;
- add personnel, including personnel to support our product development and ongoing and future commercialization efforts, and incur increases in stock compensation expense related to existing and new personnel with respect to both service-based and performance-based awards;
- evaluate market opportunities for our products and product candidates in markets outside the U.S.;
- add operational, financial and management information systems; and
- maintain, leverage and expand our intellectual property portfolio.

Our current operating plan does not contemplate other development activities that we may pursue or that all of our currently planned activities will proceed at the same pace, or that all of these activities will be fully initiated or completed during that time. We have based our estimates on assumptions that could change, and we may use our available capital resources sooner than we currently expect. We may also choose to change or increase our development, 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:

- the amount and timing of revenues from sales of ZULRESSO, the success of which will depend on the rate, degree and level of market acceptance for ZULRESSO in the treatment of PPD in the U.S., including the impact of factors such as: availability and willingness of sites of care to undertake the responsibilities necessary to administer ZULRESSO; the level of reimbursement for both ZULRESSO and the infusion in the healthcare setting and the nature of limitations on reimbursement; the number of healthcare professionals willing to prescribe ZULRESSO, healthcare settings willing to administer ZULRESSO and women with PPD who agree to be treated with ZULRESSO;
- the timing and amount of costs associated with our commercialization of ZULRESSO;
- the ability of SAGE-217 and our other clinical-stage product candidates to progress through clinical development successfully; the timing, scope and outcome of regulatory filings, reviews and approvals of such product candidates, if we are successful in our development efforts; the scope and cost of any clinical trials or other commitments required post-approval for any approved products resulting from such development efforts, if successful; and the level, timing and amount of costs associated with preparing for a potential future commercial launch of any such product candidate that is successfully developed and approved;
- the initiation, progress, timing, costs, and results of non-clinical studies and clinical trials for our existing and future product candidates; the number and length of clinical trials required by regulatory authorities to support regulatory approval; and the costs of preparing regulatory filings;
- the outcome of regulatory and other discussions and activities focused on potential pathways for advancing our product candidates in the EU and other markets outside the U.S., if we choose to proceed there, and the scope and timing of resulting decisions and plans, if any, we make to build or expand in those markets;
- the size of the PPD market and the size of the markets for which SAGE-217 and our other product candidates may be approved in the future, if successfully developed; the portion of the population in the approved indication for which our products are actually prescribed; the rate and degree of market acceptance for our products, and the pricing, availability and level of reimbursement for our products;
- the number and characteristics of the product candidates we pursue in development and the nature and scope of our discovery and development programs;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the extent to which we acquire or in-license other products and technologies; and
- our ability to establish any future collaboration arrangements on favorable terms, if at all.

Until such time, if ever, as we can generate substantial product revenue and achieve profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other sources of funding. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or in light of specific strategic considerations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and may require the issuance of warrants, which could potentially dilute the ownership interest of our stockholders. If we raise additional funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or research programs or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other means when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations and Commitments

There have been no material changes to our contractual obligations and commitments as included in our Annual Report on Form 10-K, which was filed with the SEC on February 19, 2019.

Off-Balance Sheet Arrangements

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

Application of Critical Accounting Policies

We have prepared our consolidated financial statements in accordance with accounting principles generally accepted in the U.S. Our preparation of these consolidated financial statements requires us to make estimates, assumptions, and judgments that affect the reported amounts of assets, liabilities, expenses, and related disclosures at the date of the consolidated financial statements, as well as revenue and expenses recorded during the reporting periods. We evaluate our estimates and judgments on an ongoing basis. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results could therefore differ materially from these estimates under different assumptions or conditions.

Except for the revenue recognition, inventory, cost of goods sold and accounts receivable policies described below, there have been no material changes to our critical accounting policies from those described in "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in our Annual Report on Form 10-K filed by us with the SEC on February 19, 2019.

Revenue Recognition

Effective January 1, 2017, we adopted Accounting Standards Codification ("ASC"), Topic 606, *Revenue from Contracts with Customers* ("Topic 606"). This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases. The adoption of Topic 606 had no impact on our consolidated financial statements as we did not have any revenue prior to adoption.

We received approval of ZULRESSO from the FDA in March 2019 and subsequently began to record revenues from product sales in June 2019. Prior to the second quarter of 2019, all of our revenues were derived from our collaboration agreement with Shionogi. The terms of our collaboration agreement include consideration such as non-refundable license fees, funding of research and development services, payments due upon the achievement of clinical and pre-clinical performance-based development milestones, regulatory milestones, manufacturing services to supply drug product for clinical trials, and sales-based milestones and royalties on product sales.

Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(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. 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 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, 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 an arrangement includes development and regulatory milestone payments, we evaluate whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the licensee's control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

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

We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time this is based on the use of an output or input method. To date, revenue from our collaboration agreement with Shionogi has come from an initial, up-front fee upon execution of the agreement and payment for the supply of drug product for Shionogi clinical trials.

Product revenue

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 delivery is made and 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 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 June 30, 2019, as customer invoicing generally occurs before or at the time of revenue recognition. We did not have any contract liabilities at June 30, 2019, as we did not receive any payments in advance of satisfying our performance obligations to our customers. Amounts billed or invoiced are included in accounts receivable, net on the consolidated balance sheets.

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 will update our estimates and record any necessary material adjustments in the period they are identified.

Chargebacks: We estimate chargebacks from our customers who directly purchase the product from us for fees and discounts resulting from contractual commitments to sell products to qualified healthcare providers 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 qualified healthcare providers. 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 qualified healthcare providers, 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 revenues and a current liability that is included in accrued expenses on our consolidated balance sheet. 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 revenues and accounts receivable at the time we recognize the related revenues.

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 average financial assistance amounts for ZULRESSO based on demographics for patients who have registered and been approved for assistance and record any such amounts within accrued expenses on our consolidated balance sheet. 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 associated with product that has been recognized as revenue but remains in the distribution channel at the end of each reporting period, as well as claims that have been approved but not yet paid. The 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 and other current liabilities on the consolidated balance sheets.

Product Returns: Consistent with industry practice, we offer the specialty pharmacies and specialty distributors that are our customers limited product return rights for damaged, defective or expiring product, provided it is within a specified period around the product expiration date as set forth in the applicable individual distribution agreement. We estimate the amount of our product sales that may be returned by our 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 our consolidated balance sheets. Based on the distribution model for ZULRESSO, contractual inventory limits with our customers, the product price and limited contractual return rights, we believe there will be minimal ZULRESSO returns. We will update our estimated refund liability, on at least a quarterly basis, based on actual shipments of ZULRESSO subject to contractual return rights, changes in expectations about the amount of estimated refunds or actual returns.

Inventory

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 are identical and, as a result, are both classified as inventory. Amounts in inventory associated with research and development 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. We perform an assessment of the recoverability of capitalized inventory during each reporting period and 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 loss. Inventory on-hand that will be sold beyond our normal operating cycle is classified as non-current and grouped with other assets on our consolidated balance sheets. At June 30, 2019, we did not have any such inventory.

Prior to the initial date regulatory approval is received, costs related to the production of inventory are recorded as research and development expense on our consolidated statements of operations and comprehensive loss in the period incurred. We received FDA approval for ZULRESSO on March 19, 2019 and subsequently began capitalizing costs related to inventory manufacturing.

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 revenues 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 on March 19, 2019, we 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 current period.

Accounts Receivable

Our trade accounts receivable consist of amounts due from specialty distributors and specialty pharmacies in the U.S. related to sales of ZULRESSO and have standard payment terms that generally require payment within 30 to 60 days from the invoice date. We monitor the financial performance and creditworthiness of customers so that we can properly assess and respond to changes in their credit profile. We reserve against trade accounts receivable for estimated losses that may arise from a customer’s inability to pay and any amounts determined to be uncollectible are written off against the reserve when it is probable that the receivable will not be collected.

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," in the accompanying Notes to Condensed Consolidated Financial Statements included in Item 1 of Part I of this Quarterly Report.

Item 3. Quantitative and Qualitative Disclosures about Market Risk

We had cash, cash equivalents and marketable securities of approximately $1.2 billion as of June 30, 2019. The primary objectives of our investment activities are to preserve principal, provide liquidity and maximize income without significantly increasing risk. Our primary exposure to market risk relates to fluctuations in interest rates, which are affected by changes in the general level of U.S. interest rates. Given the short-term nature of our cash, cash equivalents and marketable securities, we believe that a sudden change in market interest rates would not be expected to have a material impact on our financial condition and/or results of operations. We do not own any derivative financial instruments.

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

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

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation had a material effect on our results of operations during the six months ended June 30, 2019 and 2018.

Item 4. 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) 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, as amended 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 June 30, 2019, our management, with the participation of our principal executive officer and principal financial and accounting officer, evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934 as amended). 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 June 30, 2019, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control over Financial Reporting

During the three months ended June 30, 2019, in connection with the FDA approval of ZULRESSO, we implemented certain internal controls related to capitalization of ZULRESSO inventory costs and ZULRESSO product sales. There were no other material 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 period covered by this Quarterly Report that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II — OTHER INFORMATION

Item 1. Legal Proceedings

In the ordinary course of our business we may, from time to time, be involved in lawsuits, claims, and other legal proceedings related to contracts, employment arrangements, operating activities, intellectual property or other matters. While the outcome of any such proceedings cannot be predicted with certainty, as of June 30, 2019, we were not party to any legal proceedings that we would expect to have a material adverse impact on our financial position, results of operations or cash flow.

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 Quarterly 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 Quarterly Report, including 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 business depends heavily on our ability to successfully commercialize ZULRESSO™ (brexanolone) injection in the U.S. There is no assurance that our commercialization efforts in the U.S. with respect to ZULRESSO will be successful or that we will be able to generate revenues at the levels or on the timing we expect or at levels or on the timing necessary to support our goals.

Our lead product, ZULRESSO, was approved by the FDA in March 2019 as a treatment for postpartum depression, or PPD, and was made commercially available beginning on June 24, 2019, after 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. Our business currently depends heavily on our ability to successfully commercialize ZULRESSO in the U.S. as a treatment for PPD. We may never be able to successfully commercialize the product or meet our expectations with respect to revenues. Prior to launch of ZULRESSO, we had never marketed, sold or distributed for commercial use any pharmaceutical product. There is no guarantee that the infrastructure, systems, processes, policies, relationships and materials we have built for the commercialization of ZULRESSO in the U.S. in PPD will be sufficient for us to achieve success at the levels we expect. In addition, 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 the requirement for monitoring of the patient while ZULRESSO is administered. Patients who are prescribed ZULRESSO are required to enroll in a registry to allow us to compile additional information to further our understanding of the risk of sudden loss of consciousness during administration and management of the risk. Implementing the requirements and being ready to be certified as a site of care for administration of ZULRESSO is challenging and complex and can take a significant amount of time depending on the type of facility. We may find that this process takes longer even than the six to nine months we have estimated. Certain healthcare facilities may not have the infrastructure to support administration of ZULRESSO or to implement the REMS program or the registry, or may not be willing to do so as a result of the limitations, restrictions and other requirements related to administration of ZULRESSO or the REMS or for other reasons.

We may encounter other issues and challenges in commercializing ZULRESSO and generating revenues. For example, women with PPD who need treatment may 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 or may be concerned about the risk of excessive sedation and sudden loss of consciousness. Similarly, healthcare providers may not accept a new treatment paradigm for women with PPD, or we may not be able to compete effectively with lower cost anti-depressants. Given the mode of administration, the nature of the REMS and the limitation on the administration of ZULRESSO to a medically-supervised healthcare setting certified under the REMS, we expect that use of ZULRESSO in the U.S., will, at least initially, be focused primarily on women with more severe symptoms of PPD. We may also encounter challenges related to reimbursement of ZULRESSO, even if we have positive early indications from payors, including potential limitations in the scope, breadth, availability or amount of reimbursement covering ZULRESSO or the infusion. Similarly, healthcare settings or patients may determine that the financial burdens of treatment are not acceptable. We may face other limitations or issues related to the price of ZULRESSO. For example, healthcare settings may use on average fewer or more vials of ZULRESSO per patient than we expect and the average course of therapy cost may be different than we expect which may impact our results. Our results may also be negatively impacted if we have not adequately sized our field teams or our physician segmentation and targeting strategy is inadequate or if we encounter deficiencies or inefficiencies in our infrastructure or processes. Any of these issues could impair our ability to successfully commercialize ZULRESSO or to generate substantial revenues or profits or to meet our expectations with respect to the amount or timing of revenues or profits. Any issues or hurdles related to our commercialization efforts may materially adversely affect our business, results of operations, financial condition and prospects. There is no guarantee that we will be successful in our launch or commercialization efforts with respect to ZULRESSO.

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

Drug development is a long, expensive and uncertain process, involving a high degree of risk. Our business depends heavily on our ability to complete clinical development and non-clinical studies of SAGE-217 and our other current product candidates, and to obtain regulatory approval of and successfully commercialize those product candidates. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through non-clinical studies and clinical trials that the product candidate is safe and effective for use in each target indication. We may not be able to demonstrate the efficacy and safety of SAGE-217 or any of our other current product candidates or any future product candidate at each stage of clinical development or we may encounter issues with any non-clinical studies required for regulatory submissions. Success in non-clinical studies or in earlier stage clinical trials may not be repeated or observed in ongoing or future studies involving the same compound or other product candidates. The results of clinical trials or non-clinical studies of our product candidates at any stage may not support further development or may not be sufficient to obtain regulatory approval. For example, the FDA may ultimately decide that the design, number and type of trials, number of patients studied or results of our ongoing, planned and completed clinical trials for SAGE-217 even if positive are not sufficient for regulatory approval in MDD, PPD or any other indication, or do not support episodic treatment of MDD, which is the current focus of our development plan, or may ultimately require a development plan that supports chronic treatment based on results from clinical trials. We may not be able to meet the requirements for non-clinical data or clinical data needed to advance such a development plan. Changes in formulation, or the need to refine or scale-up the manufacturing process, for our product candidates could also delay development or require us to conduct additional clinical trials or non-clinical studies or could lead to different results than achieved with the earlier formulation or processes. We may not be able to initiate or complete our clinical trials or announce results from our clinical trials on the time-lines we expect. We may experience slower than expected enrollment and randomization of patients in our clinical trials, particularly in clinical trials where an in-patient stay or frequent site visits are required or where the patient population is small or where there are existing therapies. These types of delays can lead to delays in completion of a trial and announcement of results. There is also the potential for slower than expected clinical site initiation, delays or problems in analyzing data, and the potential need for additional analysis or data or the need to enroll additional patients in any of our clinical trials. We may also encounter delays arising from unexpected adverse events in a trial or other unexpected hurdles or issues in the conduct of any trial.

The drug development process can take many years, and may include post-marketing studies and surveillance, which will require the expenditure of substantial resources. Of the large number of drugs in development in the U.S., only a small percentage will successfully complete the FDA regulatory approval process and will be commercialized. 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 gain approval of any of our current or future product candidates, beyond ZULRESSO, we may never be able to successfully commercialize such new product or to meet our expectations with respect to revenues or profits from sales of such product.

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

We are not permitted to market any of our product candidates in the U.S. until we receive approval of an NDA from the FDA, or in any foreign countries until we receive the requisite marketing approval from such countries. Obtaining approval of an NDA in the U.S. or marketing approval in any country outside the U.S. is a complex, lengthy, expensive and uncertain process, and the FDA and regulatory authorities outside the U.S. may delay, limit or deny approval of any of our product candidates for many reasons, including, among others:

- we may not be able to demonstrate, to the satisfaction of the FDA or other regulatory authorities, that our product candidates are safe and effective in any indication and that the benefits outweigh the safety risks;
- the results of our non-clinical studies and clinical trials may be negative, or may not meet the level of statistical or clinical significance required by the FDA or regulatory authorities outside the U.S. for marketing approval;
- the FDA or regulatory authorities outside the U.S. may impose a 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, or implementation of our non-clinical studies or clinical trials are inadequate for regulatory approval or that changes in drug formulation used in our non-clinical studies or clinical trials require additional trials or studies, even if the regulatory authorities have previously reviewed and commented on the design and details of our plans;
- the FDA or regulatory or other government authorities outside the U.S. may require that we conduct additional non-clinical studies and clinical trials prior to approval or post-approval;
- the FDA or applicable foreign regulatory authorities may not approve the formulation, labeling or specifications of any of our product candidates;
- if an NDA for any of our product candidates is reviewed by an advisory committee, the advisory committee may recommend against approval of our application or may recommend that the FDA require, as a condition of approval, additional non-clinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions, and the FDA may ultimately agree with the recommendations of the advisory committee;

- the FDA or applicable foreign regulatory authorities may approve a product candidate for which we are seeking regulatory approval for a more limited patient population than we expect or with substantial use restrictions;
- as was the case with ZULRESSO, the FDA may require a REMS as a condition of approval or post-approval;
- the FDA or applicable foreign regulatory authorities may determine that the manufacturing processes or facilities of third-party contract manufacturers with which we contract do not conform to applicable requirements, including current Good Manufacturing Practices, or cGMPs; or
- the FDA or applicable foreign regulatory agencies may change their approval policies or adopt new regulations.

Any of these factors, many of which are beyond our control, could jeopardize or delay our ability to obtain regulatory approval for and successfully market our product candidates. Even if we receive marketing approval for any of our product candidates, regulatory or other governmental authorities may still impose significant restrictions, including restrictions on the indicated use or marketing, or may impose ongoing requirements for potentially costly post-approval studies. For example, 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. The FDA may recommend scheduling with respect to any of our current or future product candidates. In such event, as was the case with ZULRESSO, prior to a product launch, the DEA, will need to determine the controlled substance schedule of the product, taking into account the recommendation of the FDA. The timing of the scheduling process is uncertain and may delay our ability to market any product candidate that is successfully developed and approved.

We 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 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, including in the European Union, or EU. In order to market any product outside of the U.S., we must establish and comply with the numerous and varying safety, efficacy and other regulatory requirements of other countries. Approval procedures vary among countries and can involve additional non-clinical studies or clinical trials, additional work related to manufacturing and analytical testing on controls, and additional administrative review periods. The time required to obtain approvals in other countries might differ from that required to obtain FDA approval. Marketing approval in one country does not ensure marketing approval in another, but a failure or delay in obtaining marketing approval in one country may have a negative effect on the regulatory process in other countries. The marketing approval processes in other countries may implicate all of the risks detailed above regarding FDA approval in the U.S. as well as other risks. In particular, in many countries outside of the U.S., products must receive pricing and reimbursement approval before the product can be commercialized. Obtaining this approval may require additional studies and data, and can result in substantial delays in bringing products to market in such countries and such investment may not be justified from a business standpoint given the market opportunity or level of required investment. For example, the European Medicines Agency, or EMA, has requested that we conduct an additional clinical trial evaluating our proprietary formulation of brexanolone in the treatment of PPD to support submission of a potential marketing authorization application, or MAA, seeking approval of brexanolone in such indication. We will continue to evaluate the EMA's request in light of our overall portfolio and program priorities as well as the potential timing of development in the EU of SAGE-217. We may never file an MAA seeking approval of brexanolone or any of our other product candidates in the EU and we may never seek regulatory approval of any product or product candidate in any other country or region outside the U.S. Even if generate the data and information 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 are able to successfully develop our product candidates and obtain marketing approval in a country outside the U.S., we may not be able to obtain pricing and reimbursement approvals in such country at acceptable levels or at all, and any pricing and reimbursement approval we may obtain may be subject to onerous restrictions such as caps or other hurdles or restrictions on reimbursement. Failure to obtain marketing and pricing approval in countries outside the U.S. without onerous restrictions or limitations related to pricing or any delay or other setback in obtaining such approval, would impair our ability to market our product candidates successfully or at all in such foreign markets. Any such impairment would reduce the size of our potential market or revenue potential, which could have a material adverse impact on our business, results of operations and prospects.

Any setback or delay in obtaining regulatory approval for our product candidates in a country or region outside the U.S. where we have decided it makes business sense to proceed or in our ability to commence marketing of our products, if approved, may have a material adverse effect on our business and prospects.

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

We have received Breakthrough Therapy designation and Fast Track designation for SAGE-217 in the treatment of MDD. In the future, we may seek Fast Track, Breakthrough Therapy or PRIME designations for this product candidate in indications not yet covered or for our other product candidates. These designations do not necessarily lead to a faster development pathway or regulatory review process, and do not increase the likelihood of regulatory approval. The FDA may withdraw Fast Track designation or Breakthrough Therapy designation, and the EMA may withdraw PRIME designation, if the relevant agency believes that the designation is no longer supported by data from our clinical development programs.

The number of women with PPD, and the number of patients with the diseases and disorders for which we are developing our product candidates, has not been established with precision. If the number of women with PPD is smaller than we expect or our other assumptions with respect to the PPD market are not correct, or if ZULRESSO is actually prescribed for a smaller subset of women with PPD than we expect, our ability to achieve revenues and profits at the levels we expect could be materially adversely impacted. If the actual number of patients with the diseases or disorders we elect to pursue with our current or future product candidates is smaller than we anticipate, we may have difficulties in enrolling patients in our clinical trials which may delay or prevent development of our product candidates, and even if such product candidates are successfully developed and approved, the markets for our products may be smaller than we expect and our revenue potential and ability to achieve profitability may be materially adversely affected.

Our lead product, ZULRESSO, has been approved in the U.S. for the treatment of women with PPD. We are developing our next generation product candidate, SAGE-217, in the treatment of MDD, PPD, and other potential indications. There is no precise method of establishing the actual number of patients with any of these disorders in any geography over any time period. With respect to many of the indications in which we have developed, are developing, or plan to develop, our product candidates, we have or will provide estimates of the prevalence of the disease or disorder. Our estimates as to prevalence may not be accurate, and the actual prevalence or addressable patient population for some or all of those indications, or any other indication that we elect to pursue, may be significantly smaller than our estimates. In estimating the potential prevalence of indications we are pursuing, or may in the future pursue, including our estimates as to the prevalence of PPD and MDD, we apply assumptions to available information that may not prove to be accurate. In each case, there is a range of estimates in the published literature and in marketing studies which include estimates within the range that are lower than our estimates. For example, our estimates of the prevalence of PPD are higher than estimates reported in some of the published literature and results obtained from certain studies analyzing claims databases. We believe these differences may be the result of variations in analytical methodologies and possibly under-diagnosis of PPD as a result of lack of screening and under-reporting, and patients being reluctant to seek treatment in clinical practice. The actual number of patients with PPD, MDD, or any other indication in which we elect to pursue development of our product candidates may, however, be significantly lower than we believe. In addition, a prevalence calculation is an estimate of the total number of patients with a disease or disorder or the rate of occurrence of a disease or disorder in a population. Even if our prevalence estimates are correct, our product candidates may be developed for only a subset of patients with the relevant disease or disorder or our products, if approved, may be indicated or used for only a subset. For example, the IV infusion mode of administration for ZULRESSO; limitations on sites of care for administration of ZULRESSO to REMS certified healthcare settings; the requirement for a registry as part of the REMS, and the other requirements of the REMS; the risk of excessive sedation and sudden loss of consciousness; and reimbursement restrictions or the cost of therapy compared to lower cost antidepressants may limit the type of women who are prescribed ZULRESSO or who actually receive treatment to those patients with more severe symptoms of PPD even beyond the initial launch period. In the event the number of patients with the diseases and disorders we are studying is significantly lower than we expect, we may have difficulties in enrolling patients in our clinical trials which may delay or prevent development of our product candidates. If 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 revenues or profits.

If serious adverse events or other undesirable side effects are identified during the use of any of our marketed products or product candidates, including commercial use or use in clinical trials, emergency-use cases, investigator sponsored trials, expanded access programs, or non-clinical studies, it may adversely affect market acceptance of an approved product or further development or our ability to gain regulatory approval of any product candidate.

Undesirable side effects caused by ZULRESSO in commercial use or in any further clinical trials, nonclinical studies, expanded access programs or investigator-initiated studies could limit market acceptance of the product, or cause the FDA or other regulatory authorities to add significant restrictions on use or cause us to withdraw the product from the market and could have other material adverse effects on our business. Undesirable side effects caused by any of our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials, or could make it more difficult for us to enroll patients in our clinical trials. If serious adverse events or other undesirable side effects, or unexpected characteristics of any of our product candidates are observed in clinical trials, emergency-use cases, investigator sponsored clinical trials, expanded access, or non-clinical studies, further clinical development of such product candidate may be delayed or we may not be able to continue development of such product candidates at all or we may also need to discontinue development of other product candidates. Even if development continues, such adverse events or other undesirable side effects, or unexpected characteristics of any of our product candidates may result in delay or denial of FDA or other regulatory approval or result in substantial restrictions on such approval.

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

Positive results from non-clinical studies and clinical trials of our product candidates may not necessarily be predictive of the results we may obtain from subsequent non-clinical studies or clinical trials using the same product candidate or other product candidates. By way of example, our results in an earlier clinical trial were not replicated in our Phase 3 clinical trial of ZULRESSO in super-refractory status epilepticus. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later-stage clinical trials after achieving positive results in early-stage development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, non-clinical findings made while clinical trials were underway or safety or efficacy observations made in non-clinical studies and clinical trials that are different than in earlier trials or studies, including previously unreported or otherwise unexpected adverse events. For example, we may observe safety issues in clinical studies of our product candidates that we did not observe or appreciate in earlier stage clinical studies or in non-clinical studies. The results from non-clinical animal models may not be replicated in clinical trials. Many drug candidates, including many targeting CNS disorders, with promising non-clinical profiles have failed to demonstrate similar safety, non-toxicity and efficacy in humans. Many drugs have failed to replicate efficacy results in larger or more complex later stage trials. For example, the results of our Phase 2 placebo-controlled clinical trial of SAGE-217 in MDD may not be replicated in ongoing and planned Phase 3 clinical trials in MDD which will involve a larger number of patients. Moreover, non-clinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in non-clinical studies and clinical trials nonetheless failed to obtain FDA approval. If we fail to produce positive results in our planned non-clinical studies or clinical trials of any of our product candidates, the development timeline and regulatory approval and commercialization prospects for our product candidates, and, correspondingly, our business and financial prospects, would be materially adversely affected.

Failures or delays in the commencement or completion of our ongoing and planned clinical trials of our 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.

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 or future clinical trials will begin or be completed, and results announced, as planned or expected, if at all, as the commencement and completion of clinical trials and announcement of results can be delayed or prevented for a number of reasons, including, among others:

- denial by the FDA or other regulatory authority of permission to proceed with our planned clinical trials or any other clinical trials we may initiate, or placement of a clinical trial on hold;
- delays in filing or receiving approvals of additional investigational new drug applications, or INDs, that may be required;
- negative results from our ongoing non-clinical studies or clinical trials;
- challenges in identifying, recruiting and enrolling patients to participate in clinical trials, including, in some cases, due to: the small size of the patient population being studied; the lack of proximity of some patients to trial sites; challenges in meeting regulatory and material requirements to commence clinical trials in countries outside the U.S.; eligibility criteria for the clinical trial; challenges associated with the nature of the clinical trial protocol; the availability of existing treatments for the relevant disease; the requirement for in-patient stays with respect to some of our trials; and competition from other clinical trial programs for similar indications, any of which could delay enrollment of patients in ongoing or future clinical trials of our product candidates;
- delays in reaching or failing to reach agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- inadequate quantity or quality of supplies of a product candidate or other materials necessary to conduct clinical trials, for example as a result of delays in defining, refining and implementing the manufacturing process for materials used in pivotal trials or for the manufacture of larger quantities or other delays or issues arising in the manufacturing of sufficient supply of finished drug product;
- difficulties obtaining Institutional Review Board, or IRB, approval, and equivalent approval for sites outside the U.S., to conduct a clinical trial at a prospective site or sites;
- delays or problems in analyzing data, or the need for additional analysis or data or the need to enroll additional patients;
- the occurrence of serious adverse events or unexpected drug-related side effects experienced by patients in a clinical trial or unexpected results in ongoing non-clinical studies;
- delays in validating endpoints utilized in a clinical trial;
- our inability to satisfy the requirements of the FDA to commence clinical trials, including chemistry, manufacturing and control, or CMC, requirements, or other FDA requirements prior to the initiation of a clinical trial;
- the FDA or applicable regulatory authorities outside the U.S. disagreeing with our clinical trial design and our interpretation of data from clinical trials, or changing the requirements for approval even after the regulatory authority has reviewed and commented on the design for our clinical trials;
- reports from non-clinical or clinical testing of other CNS therapies that raise safety or efficacy concerns; and
- difficulties retaining patients who have enrolled in a clinical trial but may be prone to withdraw due to rigors of the clinical trials, lack of efficacy, side effects, personal issues or loss of interest.

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

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

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

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

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

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

- have staffing difficulties;
- fail to comply with contractual obligations;
- fail to comply with current Good Clinical Practices, or GCPs, or experience other regulatory compliance issues;

- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical trials, and may subject us to unexpected cost increases that are beyond our control. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific requirements and standards, and our reliance on CROs does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with regulations and guidelines, including 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 and comparable foreign regulatory authorities for any products in clinical development. The FDA enforces GCP regulations through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we or our CROs or clinical sites fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA or applicable regulatory authorities outside the U.S. will determine that our clinical trials and all of our clinical sites, CROs and contract laboratories comply with GCPs. In addition, our clinical trials must be conducted with product candidates produced under GMPs regulations. Our failure or the failure of our CROs or contract manufacturers to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process, and could also subject us to enforcement action up to and including civil and criminal penalties.

If any of our relationships with third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, and we are unable to rely on clinical data collected, we could be required to repeat, extend the duration of, or increase the size of our clinical trials and this could significantly delay or prevent regulatory approval of such 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.

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 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 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 will also rely on our contract manufacturers to manufacture sufficient quantities of SAGE-217, SAGE-324, and SAGE-718 and our other product candidates for ongoing and future clinical trials and non-clinical studies, and to scale our manufacturing processes for later stage clinical trials, if our development efforts at each stage are successful. We expect our contract manufacturers to comply with cGMPs in the manufacture of our products. The facilities used by our contract manufacturers to manufacture the active pharmaceutical ingredient and final drug product must typically complete a pre-approval inspection by the FDA and other comparable foreign regulatory agencies to assess compliance with applicable requirements, including cGMPs, after we submit the relevant NDA or equivalent foreign regulatory submission to the applicable regulatory agency. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or applicable foreign regulatory agencies, and pass regulatory inspections, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities with respect to our products. In addition, we have no direct control over our contract manufacturers' ability to maintain adequate quality control, quality assurance and qualified personnel. Furthermore, all of our third-party contract manufacturers are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our third-party contract manufacturers to regulatory risks for the production of such materials and products. As a result, failure to satisfy the regulatory requirements for the production of those materials and products may affect the regulatory clearance of our contract manufacturers' facilities generally. If the FDA or an applicable foreign regulatory agency determines now or in the future that these facilities for the manufacture of our 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.

We have a long-term supply agreement with our contract manufacturer with respect to ZULRESSO drug substance. We do not yet have long-term supply agreements in place with our contract manufacturers with respect to ZULRESSO drug product or, with respect to drug substance or drug product, for any of our product candidates, and each batch of ZULRESSO drug product and each batch of drug substance and drug product for our other product candidates is individually contracted through a purchase order governed by our master service and quality agreements. We have an inventory of ZULRESSO drug product and drug substance in place to help mitigate any potential supply risks, but there is no guarantee that this inventory will be adequate. If our existing contract manufacturers are not willing to enter into long-term supply agreements, or are not willing or are unable to supply drug substance or drug product to us, and we engage new contract manufacturers, such contractor manufacturers for any approved product must scale up the manufacturing process, complete validation batches, pass an inspection by the FDA and other applicable foreign regulatory agencies, and be approved by regulatory authorities as our manufacturer before we are able to use drug product or drug substance they manufacture for commercial purposes which could result in significant delays or gaps in product availability. We plan to continue to rely upon contract manufacturers to manufacture commercial quantities of our products, if approved. If we are unable to maintain arrangements for third-party manufacturing, or are unable to do so on commercially reasonable terms, or are unable to obtain timely regulatory approvals in connection with our contract manufacturers, we may not be able to successfully commercialize our approved and successfully complete development of our current or future product candidates.

If we have not built, or do not maintain, sufficient sales, marketing and distribution capabilities to market, sell and distribute ZULRESSO or do not build sufficient capability with respect to any of our current or future product candidates, if successfully developed and approved, or if we are unable to achieve market acceptance for such products, our business, results of operations, financial condition and prospects will be materially adversely affected.

ZULRESSO is the first product we have marketed, sold and distributed for commercial use. There is no guarantee that the systems, processes, policies, relationships and materials we have built will be sufficient for successful commercialization of the product in the U.S. as a treatment for PPD. If we have not established adequate sales, marketing and distribution capabilities for ZULRESSO, or do not establish capabilities, whether independently or with third parties, for any of future approved products, or if we are unable to do so on commercially reasonable terms, our business, results of operations, financial condition and prospects will be materially adversely affected. For example, administration of ZULRESSO is limited to medically-supervised healthcare settings that are certified under a REMS program and meet the other requirements of the REMS, including the requirement for monitoring of the patient while ZULRESSO is administered. In addition, patients receiving ZULRESSO are required, as part of the REMS program, to enroll in a registry to gather information to help further characterize the risk of excessive sedation and sudden loss of consciousness during administration of ZULRESSO and on management of the risk. Implementing these requirements is challenging and complex and may take time depending on the site. Certain healthcare settings may not have the infrastructure to support administration of ZULRESSO or to implement the REMS program or the registry, or may not be willing to do so as a result of the limitations, restrictions and other requirements. We may encounter issues, delays or other challenges in commercializing ZULRESSO or any of our other product candidates that are successfully developed and approved. For example, our results may be negatively impacted if we have not adequately sized our field teams or if our physician segmentation and targeting strategy is inadequate or if we encounter deficiencies or inefficiencies in our infrastructure or processes. Women with PPD who need treatment may find it too onerous to undergo an infusion or to be treated at a healthcare facility overnight for the length of stay required for treatment or to be enrolled in the registry or may be concerned about the risk of excessive sedation and sudden loss of consciousness. Similarly, healthcare providers may not accept a new treatment paradigm for women with PPD, or we may not be able to compete effectively with lower cost anti-depressants. We may encounter unexpected limitations in the scope, breadth or amount of reimbursement covering ZULRESSO or the infusion, or other limitations or issues related to the price. We may never seek or be able to generate sufficient data to sufficiently satisfy the FDA so as to permit in the future administration in the home setting even with monitoring and supervision requirements. Any of these issues could impair our ability to successfully commercialize the product or to generate substantial revenues or profits or to meet our expectations with respect to the amount or timing of revenues or profits. We may encounter similar or different commercialization efforts with respect to any of our other product candidates, if successfully developed and approved. There is no guarantee that we will be successful in our commercialization efforts with respect to ZULRESSO or with respect to any other product candidate that may be approved in the future.

ZULRESSO or any future product, 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 their sales.

The commercial success of ZULRESSO or of any of our 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 the medical community, including physicians, patients and healthcare payors, and reimbursement at sufficient levels. Market acceptance will depend on a number of factors, including, among others:

- the efficacy of our products as demonstrated in clinical trials, and, if required by any applicable regulatory authority in connection with the approval for the applicable indications, our ability to demonstrate in clinical trials that our products provide patients with incremental health benefits, as compared with other available CNS therapies;
- limitations or warnings contained in the labeling approved for our products by the FDA or other applicable regulatory authorities;
- the clinical indications and size of patient populations for which our products are approved;
- availability of alternative treatments already approved or expected to be commercially launched in the near future;
- the potential and perceived advantages and limitations of our products over current treatment options or alternative treatments, including future alternative treatments, including in the case of ZULRESSO, the impact of limitations arising from the IV infusion mode of administration, the length of stay required for treatment, restrictions on site of care to REMS certified healthcare facilities and other requirements of the REMS, the risk of excessive sedation and loss of consciousness during administration, and the availability of lower cost antidepressants;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments;
- pricing and cost effectiveness;
- the effectiveness of our sales and marketing deployment and strategies;
- our ability to increase awareness of our approved products through marketing efforts;
- the availability of sufficient third-party coverage or reimbursement, including in the case of ZULRESSO for both the product and the cost of the infusion; or
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage or as co-pay amounts under third party coverage.

If ZULRESSO, or any of our 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 may not do so on the timelines we expect. Before granting reimbursement approval, healthcare payors may require us to demonstrate that our product candidates, in addition to treating these target indications, also provide incremental health benefits to patients or healthcare costs savings. Our efforts to educate the medical community and third-party payors about the benefits of ZULRESSO or any future approved products, to the extent permitted, may require significant resources and may never be successful.

ZULRESSO or our current or future product candidates or any future products, if successfully developed and approved, may cause undesirable side effects that limit the commercial profile or result in other significant negative consequences for approved products; or 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.

Undesirable side effects caused by ZULRESSO or any future products, if and when approved, could limit the commercial profile of such product or result in significant negative consequences such as a more restrictive label or other limitations or restrictions.

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

Clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients and limited duration of exposure, certain side effects of ZULRESSO or of our current or future product candidates may only be uncovered with a significantly larger number of patients exposed to the product, and those side effects could be serious or life-threatening. If we or others identify undesirable side effects caused by ZULRESSO or any future approved product (or any other similar products), a number of potentially significant negative consequences could result, including:

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

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

Even after marketing approval of a product, we 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 elect, or are required, to proceed with pediatric studies of any of our product candidates in any indication, regulatory authorities may also require additional nonclinical studies or clinical trials be completed prior to commencement of such pediatric studies.

As was the case with brexanolone, the FDA may recommend controlled substance scheduling for our current or future product candidates. In such event, the DEA will need to determine the controlled substance schedule taking into account the recommendation of the FDA. The process may delay our ability to market any such product if it is approved.

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 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 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, including requiring withdrawal of such products from the market or suspension of manufacturing. If we, our approved products, our product candidates, or the manufacturer 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 could emerge that adversely affect the amount of revenue we are able to generate from the sale of ZULRESSO or any of our 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 product candidates or address similar markets. It is probable that the number of companies seeking to develop products and therapies similar to our products will increase.

Currently, there are no pharmacological therapies specifically approved for the treatment of PPD 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 development candidate, SAGE-217, is in Phase 3 development for MDD and PPD. MDD patients are typically treated with a variety of antidepressant medications, including SSRIs and SNRIs. If successfully developed and approved, SAGE-217 may also face competition from esketamine which is approved in the treatment of TRD. A number of companies are developing product candidates intended for the treatment of MDD, including NMDA receptor antagonists or partial antagonists such as apimostinel and the opioid receptor antagonist combination product, buprenorphine/samidorphan.

In the field of neuroactive steroids focused specifically on modulation of GABAA receptors, we also face competition from Marinus Pharmaceuticals, Inc., or Marinus. Marinus is developing a form of ganaxolone, a known GABAA positive allosteric modulator neuroactive steroid.

A number of companies are working to develop products targeted at the NMDA receptor, both antagonists and agonists.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and human resources than we do, and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of treatments and the commercialization of those treatments. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. We expect competition in the indications we are pursuing will focus on efficacy, safety, convenience, availability, and price. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

We have an existing collaboration, and may seek to establish additional collaborations, related to our development and commercialization of product candidates. Our existing and future collaborations, if any, may not lead to the successful development or commercialization of product candidates. If we determine that future collaborations are important to our business, and we are not able to establish future collaborations on commercially reasonable terms, we may have to alter our development and commercialization plans or expand our internal efforts and growth.

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

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

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the U.S., the potential market for the applicable product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to intellectual property protection or ownership of technology, which can exist if there is a challenge to such intellectual property or ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for our product candidate. The terms of any collaboration or other arrangements that we may establish may not be favorable to us.

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

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable or unwilling to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization in some or all markets or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense, including potentially increasing our infrastructure and investment outside the U.S. Such efforts may require diversion of a disproportionate amount of our attention away from other day-to-day activities, and require devotion of a substantial amount of our time to managing these expansion activities. If we elect to increase our expenditures to fund development or commercialization activities on our own that we had planned to develop in collaboration with a third party, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

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

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

Because we have limited financial and management resources, we focus on a limited number of clinical and research programs and product candidates and are currently focused on certain CNS disorders. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable drugs. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through future collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which may have a material adverse effect on our business.

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

The Medicaid Drug Rebate Program and other governmental programs impose obligations to report pricing figures to the federal government. We participate in the Medicaid Drug Rebate Program, meaning that we are subject to these price reporting and other compliance obligations. 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.

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

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

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

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

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

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

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

In order to be eligible to have our products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by the Department of Veterans Affairs, or VA, Department of Defense, or DoD, Public Health Service, and Coast Guard (the “Big Four agencies”) and certain federal grantees, we 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 outpatient drugs available for procurement on an FSS contract and charge a price to the Big Four agencies that is no higher than the Federal Ceiling Price, or FCP, which is a price calculated pursuant to a statutory formula. The FCP is derived from a calculated price point called the “non-federal average manufacturer price”, or Non-FAMP, which we 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 penalties of $181,071 for each item of false information. The FSS contract also contains extensive disclosure and certification requirements.

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

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

We are subject to additional healthcare statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we conduct our business. 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 similar role with respect to any of our future products, 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, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid.
- The federal False Claims Act imposes criminal and civil penalties, including those from civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease, or conceal an obligation to pay money to the federal government.
- The federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.
- The federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services.
- The federal transparency requirements, sometimes referred to as the “Sunshine Act”, under the Patient Protection and Affordable Care Act, require manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children’s Health Insurance Program to report to the Department of Health and Human Services information related to physician payments and other transfers of value and physician ownership and investment interests.
- Analogous state laws and regulations, such as state anti-kickback and false claims laws and transparency laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures and drug pricing.
- 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 could be costly. It is possible that governmental authorities will conclude that our business practices and arrangements do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our practices or operations, including anticipated activities to be conducted by our 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. 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.

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

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

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

The FDA and other regulatory and enforcement agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. If we are found to have improperly promoted off-label uses, we may become subject to significant liability.

The FDA and other regulatory and enforcement agencies strictly regulate the promotional claims that may be made about prescription products, and enforce laws and regulations prohibiting the promotion of off-label uses. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the approved labeling of the product. If we are found to have promoted off-label uses for any product, we may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of ZULRESSO or any of our future approved products in compliance with applicable laws, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

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

Brexanolone, which is the active ingredient of ZULRESSO is regulated as a Schedule IV controlled substance. The FDA may similarly recommend that any current or future product candidates that we successfully develop be regulated as controlled substances. In such event, then before we can commercialize any such product, the DEA will need to determine the controlled substance schedule, taking into account the recommendation of the FDA. This could delay our marketing of a product candidate and could potentially shorten the benefit of any regulatory exclusivity periods for which we may be eligible. The DEA has established certain registration, security, recordkeeping, reporting, storage, distribution, importation, exportation, inventory, quota and other requirements administered by the DEA with respect to “controlled substances” as defined in the Controlled Substances Act of 1970, or CSA, and the implementing regulations. These requirements may be applicable to us, to our third-party manufacturers and to distributors, prescribers and dispensers of our product candidates. The DEA regulates the handling of controlled substances through a closed chain of distribution. This control extends to the equipment and raw materials used in their manufacture and packaging, in order to prevent loss and diversion into illicit channels of commerce. A number of states and foreign countries also independently regulate these drugs as controlled substances.

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

If determined to be controlled substances, the manufacturing, shipping, storing, selling and using of the products will be subject to an additional regulation. Distribution, prescribing and dispensing of these drugs are also regulated.

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

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

Reimbursement policies could limit market acceptance and sales of ZULRESSO or any of our product candidates, if successfully developed and approved.

Market acceptance and sales of ZULRESSO and future approved products will depend on reimbursement policies and may be affected by healthcare reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels for those medications. Cost containment is a primary concern in the U.S. healthcare industry and elsewhere. Government authorities and these third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. The pricing and reimbursement environment for our products, if approved, is challenging, and may become even more challenging in the future due to, among other reasons, policies advanced by the current presidential administration or federal agencies, new healthcare legislation passed by Congress or fiscal challenges faced by all levels of government health administration authorities. We cannot be sure that reimbursement will be available for ZULRESSO or for any future approved product from a sufficient number of payors, and, if reimbursement is available, that the level and terms of such reimbursement will be sufficient. Payors may adopt restrictions on reimbursement such as requiring patients to try other lower cost therapies prior to being prescribed our product or to meet criteria more restrictive than the approved label for our product. These restrictions might impede appropriate use of our product for the approved indication. Reimbursement may impact the demand for, or the price of, our products. If reimbursement is not available on acceptable terms or is available only at limited levels, we may not be able to successfully commercialize ZULRESSO or any future approved product, or generate revenues at the levels we expect.

Governments outside the U.S. may impose strict price controls, which may adversely affect our revenues, if any.

The pricing of prescription pharmaceuticals is also subject to governmental control outside the U.S. 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. In such countries, pricing negotiations with governmental authorities can take considerable time after receipt of regulatory approval for a product. In addition, 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 some countries, we may be required to conduct a clinical study or other studies that compare the cost-effectiveness of a product candidate to other available therapies in order to obtain or maintain reimbursement or pricing approval, which is time-consuming and costly. We cannot be sure that such prices and reimbursement will be acceptable to us or our strategic partners. 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 strategic partners and the potential profitability of our products in those countries would be negatively affected.

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

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

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

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

Risks Related to Our Intellectual Property Rights

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

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

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

We have one issued U.S. patent covering the method of treating PPD using brexanolone i.v. which is exclusively licensed to Sage by The Regents of the University of California, and will expire in 2033. Recently a U.S. patent covering the formulation of brexanalone i.v. issued, which will also expire in 2033. We currently have one issued U.S. patent covering the composition of matter of SAGE-217, one issued U.S. patent covering methods of using SAGE-217, one issued U.S. patent covering the composition of matter of SAGE-689, and one issued U.S. patent covering methods of using SAGE-689. We also have granted European patents covering SAGE-217, SAGE-689 and SAGE-718. We cannot provide any assurances that any of our pending patent applications will mature into issued patents and, if they do, that such patents will be enforceable or include, claims with a scope sufficient to protect our product candidates or otherwise provide any competitive advantage. For example, the 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 practicing alternative methods. There can be no assurance that any such alternative formulations will not be equally effective as ZULRESSO. Moreover, other parties have developed technologies that may be related or competitive to our approach, and may have filed or may file patent applications and may have received or may receive patents that may overlap or conflict with our patent applications, either by claiming the same methods or formulations or by claiming subject matter that could dominate our patent position. Such third-party patent positions may limit or even eliminate our ability to obtain patent protection for certain inventions.

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

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

Our ability to enforce our patent rights depends on our ability to detect infringement. It is difficult to detect infringers who do not advertise the components that are used in their products. Moreover, it may be difficult or impossible to obtain evidence of infringement in a competitor’s or potential competitor’s product. Any litigation to enforce or defend our patent rights, even if we were to prevail, could be costly and time-consuming, and would divert the attention of our management and key personnel from our business operations. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded if we were to prevail may not be commercially meaningful.

In addition, proceedings to enforce or defend our patents, if and when issued, could put our patents at risk of being invalidated, held unenforceable, or interpreted narrowly. Such proceedings could also provoke third parties to assert claims against us, including that some or all of the claims in one or more of our patents are invalid or otherwise unenforceable. If any of our patents, if and when issued, covering our product candidates are invalidated or found unenforceable, our financial position and results of operations may be materially and adversely impacted. In addition, if a court found that valid, enforceable patents held by third parties covered our product candidates, our financial position and results of operations may also be materially and adversely impacted.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- any of our pending patent applications, if issued as a patent, will include claims having a scope sufficient to protect our current product candidates or any other products or product candidates;
- any of our pending patent applications will issue as patents at all;
- we will be able to successfully commercialize 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 be found to ultimately be valid and enforceable;
- any patents issued to us will provide a basis for an exclusive market for our commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties;
- we will develop additional proprietary technologies or product candidates that are separately patentable; or
- that our commercial activities or products will not infringe upon the patents or proprietary rights of others.

We may rely upon unpatented trade secrets, and depend on unpatented know-how and continuing technological innovation to develop and maintain our competitive position, which we seek to protect, in part, by confidentiality agreements with our employees and our CROs, collaborators and consultants. It is possible that technology relevant to our business will be independently developed by a person that is not a party to such an agreement. Furthermore, if the employees and consultants who are parties to these agreements breach or violate the terms of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets through such breaches or violations. Further, our trade secrets could otherwise become known or be independently discovered by our competitors.

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

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

The pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may allege that our product candidates or the use of our technologies infringes patent claims or other intellectual property rights held by them or that we are employing their proprietary technology without authorization. As we continue to develop 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 candidates may infringe, or which such third parties claim are infringed by our technologies. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could have a material adverse effect on us. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. Patent litigation is costly and time-consuming. Any claim relating to intellectual property infringement that is successfully asserted against us may require us to pay substantial damages, including treble damages and attorney's fees if we are found to be willfully infringing another party's patents, for past use of the asserted intellectual property and royalties and other consideration going forward if we are forced to take a license. In addition, if any such claim were successfully asserted against us and we could not obtain such a license, we may be forced to stop or delay developing, manufacturing, selling or otherwise commercializing our product candidates. In the case of trademark claims, if we are found to be infringing, we may be required to redesign, or rename, some or all of our product candidates to avoid infringing the intellectual property rights of third parties, which may not be possible and, even if possible, could be costly and time-consuming. Even if we are successful in these proceedings, we may incur substantial costs and divert management time and attention in pursuing these proceedings, which could have a material adverse effect on us.

Any of these risks coming to fruition could have a material adverse effect on our business, results of operations, financial condition and prospects.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We enter into confidentiality and intellectual property assignment agreements with our employees, consultants, CROs, outside scientific collaborators, and other advisors. These agreements generally provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, these agreements may not be honored and may not effectively assign intellectual property rights to us. For example, even if we have a consulting agreement in place with an academic advisor pursuant to which such academic advisor is required to assign to us any inventions developed in connection with providing services to us, such academic advisor may not have the right to assign such inventions to us, as it may conflict with his or her obligations to assign all such intellectual property to his or her employing institution or another party.

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

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

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

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Even if the patent applications we own or license are issued, competitors may infringe these patents. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the U.S.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.

If we or one of our licensing partners initiated legal proceedings against a third party to enforce a patent, if and when issued, covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the U.S., defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include alleged failures to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for unenforceability assertions include allegations that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the U.S. or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *ex parte* reexamination, or *inter partes* review and equivalent proceedings in foreign jurisdictions, e.g., opposition proceedings. Such proceedings could result in revocation or amendment of our patents in such a way that they no longer cover our product candidates or competitive products. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

We will not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

Filing patent applications and prosecuting and defending patents on product candidates in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the U.S. could be less extensive than those in the U.S., assuming that rights are obtained in the U.S. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling or importing products made using our inventions in and into the U.S. or other jurisdictions. The statutory deadlines for pursuing patent protection in individual foreign jurisdictions are based on the priority date of each of our patent applications.

Competitors may use our technologies in jurisdictions where we do not pursue patent protection. They may pursue and obtain their own patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the U.S. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the U.S. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biotechnology and pharmaceuticals. For example, a 2018 report from the Office of the U.S. Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. This could make it difficult for us to stop the infringement of our patents, if obtained, or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

Furthermore, proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

For certain of our product candidates, we are dependent on licensed intellectual property. If we were to lose our rights to licensed intellectual property, we may not be able to continue developing or commercializing certain of our products or product candidates. If we breach any of the agreements under which we license the use, development and commercialization rights to our product candidates or technology from third parties or, in certain cases, we fail to meet certain development deadlines, we could lose license rights that are important to our business.

We are a party to a number of license agreements under which we are granted rights to intellectual property that are important to our business and we expect that we may need to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose on us, various development, regulatory and/or commercial diligence obligations, payment of milestones and/or royalties and other obligations. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license. Our business could suffer, for example, if any current or future licenses terminate, if the licensors fail to abide by the terms of the license, if the licensed patents or other rights are found to be invalid or unenforceable, or if we are unable to enter into necessary licenses on acceptable terms.

As we have done previously, we may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we cannot provide any assurances that third-party patents do not exist that might be enforced against our current product candidates or future products in the absence of such a license. We may fail to obtain any of these licenses on commercially reasonable terms, if at all. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation.

Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patent and other rights to third parties under collaborative development relationships;
- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates, and what activities satisfy those diligence obligations; and
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

We have entered into several licenses to support our various programs.

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

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

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

We may enter into additional licenses to third-party intellectual property that are necessary or useful to our business. Our current licenses and any future licenses that we may enter into impose various royalty payment, milestone, and other obligations on us. For example, the licensor may retain control over patent prosecution and maintenance under a license agreement, in which case, we may not be able to adequately influence patent prosecution or prevent inadvertent lapses of coverage due to failure to pay maintenance fees. If we fail to comply with any of our obligations under a current or future license agreement, the licensor may allege that we have breached our license agreement, and may accordingly seek to terminate our license. In addition, future licensors may decide to terminate their licenses with us at will. Termination of any of our current or future licenses could result in our loss of the right to use the licensed intellectual property, which could materially adversely affect our ability to develop a product candidate or and 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 may have been generated using U.S. government funds. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if the government determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). The U.S. government also has the right to take title to these inventions if we fail, or the applicable licensor fails, to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. In addition, the U.S. government may acquire title to these inventions in any country in which a patent application is not filed within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us, or the applicable licensor, to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the U.S. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the U.S. or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property.

If we enter into future arrangements involving government funding, and we discover compounds or drug candidates as a result of such funding, intellectual property rights to such discoveries may be subject to the applicable provisions of the Bayh-Dole Act.

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

Marketing exclusivity provisions under the Federal Food, Drug, and Cosmetic Act, or FDCA, can delay the submission or the approval of certain marketing applications by other companies for a product with the same active moiety as a product we may in the future sell. The FDCA provides a five-year period of non-patent marketing exclusivity within the U.S. to the first applicant to obtain approval of an NDA for a new chemical entity, or NCE. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA also provides three years of marketing exclusivity for a full NDA, or supplement to an existing NDA, if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. We have obtained NCE exclusivity for brexanolone, and plan to seek NCE exclusivity for our current and future product candidates. There is also 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 to 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 future U.S. patents we own or license may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. Even if, at the relevant time, we have a valid issued patent covering our product, we may not be granted an extension if we were, for example, to fail to apply within applicable deadlines, to fail to apply prior to expiration of relevant patents or otherwise to fail to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, and we do not have any other exclusivity, our competitors may obtain approval of competing products following our patent expiration and our ability to generate revenues could be materially adversely affected.

If we do not have adequate patent protection or other exclusivity for our products, our business, financial condition or results of operations could be adversely affected.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the U.S. has recently enacted and is currently implementing wide-ranging patent reform legislation: the Leahy-Smith America Invents Act, referred to as the America Invents Act. The America Invents Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. It is not yet clear what, if any, impact the America Invents Act will have on the operation of our business. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of any patents that may issue from our patent applications, all of which could have a material adverse effect on our business and financial condition.

In addition, recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. The full impact of these decisions is not yet known. For example, on March 20, 2012 in *Mayo Collaborative Services, DBA Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc.*, the Court held that several claims drawn to measuring drug metabolite levels from patient samples and correlating them to drug doses were not patentable subject matter. The decision appears to impact diagnostics patents that merely apply a law of nature via a series of routine steps and it has created uncertainty around the ability to obtain patent protection for certain inventions. Additionally, on June 13, 2013 in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the Court held that claims to isolated genomic DNA are not patentable, but claims to complementary DNA molecules are patent eligible because they are not a natural product. The effect of the decision on patents for other isolated natural products is uncertain. On June 19, 2014 in *Alice Corporation Pty. Ltd. v. CLS Bank International, et al.*, a case involving patent claims directed to a method for mitigating settlement risk, the Court held that the patent eligibility of claims directed to abstract ideas, products of nature, and laws of nature should be determined using the same framework set forth in Prometheus. The U.S. PTO recently issued a set of guidelines setting forth procedures for determining subject matter eligibility of claims directed to abstract ideas, products of nature, and laws of nature in line with the Prometheus, Myriad, and Alice decisions. The guidance does not limit the application of Myriad to DNA but, rather, applies the decision to other natural products.

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

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

Most of our employees have been previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. We also engage advisors and consultants who are concurrently employed at universities or who perform services for other entities.

Although we are not aware of any claims currently pending against us, we may be subject to claims that we or our employees, advisors or consultants have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of a former employer or other third party. We may be subject to claims that an employee, advisor or consultant performed work for us that conflicts with that person's obligations to a third party, such as an employer, and thus, that the third party has an ownership interest in the intellectual property arising out of work performed for us. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. If we fail in defending such claims, in addition to paying monetary claims, we may lose valuable intellectual property rights or personnel. A loss of key personnel or their work product could hamper or prevent our ability to develop and commercialize our product candidates, which would materially adversely affect our efforts and results.

Proposed legislation in Congress, if passed into law, could limit the patent exclusivity on our products or facilitate earlier entry of generic competition.

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 limit the duration of patent exclusivity on ZULRESSO or any future products or result in earlier entry into the market of generic versions of our drugs.

Numerous factors may limit any potential competitive advantage provided by our intellectual property rights.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, provide a barrier to entry against our competitors or potential competitors, or permit us to maintain our competitive advantage. Moreover, if a third party has intellectual property rights that cover the practice of our technology, we may not be able to fully exercise or extract value from our intellectual property rights. The following examples are illustrative:

- others may be able to develop and/or practice technology that is similar to our technology or aspects of our technology but that is not covered by the claims of any patents that have, or may, issue from our patent applications;
- we might not have been the first to make the inventions covered by a pending patent application that we own;
- we might not have been the first to file patent applications covering an invention;
- others may independently develop similar or alternative technologies without infringing our intellectual property rights;
- pending patent applications that we own or license may not lead to issued patents;
- patents, if issued, that we own or license may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- third parties may compete with us in jurisdictions where we do not pursue and obtain patent protection;
- we may not be able to obtain and/or maintain necessary or useful licenses on reasonable terms or at all;
- third parties may assert an ownership interest in our intellectual property and, if successful, such disputes may preclude us from exercising exclusive rights over that intellectual property;
- we may not develop or in-license additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business and results of operations.

General Company-Related Risks

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

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

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

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

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

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

The 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 acts. If we become subject to product liability claims and cannot successfully defend ourselves against them, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in, among other things:

- withdrawal of patients from our clinical trials, or difficulty in enrolling clinical trials;
- substantial monetary awards to patients or other claimants;
- decreased demand for our 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.

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

As a public company, we incur significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the Securities and Exchange Commission and The NASDAQ Stock Market have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations cause us to incur significant legal and financial compliance costs, and make some activities more time-consuming and costly.

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

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

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

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

As of December 31, 2018, we had federal and state net operating loss carryforwards of $755.0 million and $760.7 million, respectively, which begin to expire in 2031 and 2030, respectively. As of December 31, 2018, we also had federal and state research and development tax credit carryforwards of $20.3 million and $4.1 million, respectively, which begin to expire in 2031 and 2027, respectively. As of December 31, 2018, we had federal orphan drug tax credit carryforwards of $40.0 million, which begin to expire in 2034. Under Section 382 of the Code, and similar state tax law, changes in our ownership may limit the amount of our net operating loss carryforwards and tax credit carryforwards that could be utilized annually to offset our future taxable income, if any. This limitation would generally apply in the event of a cumulative change in ownership of our company of more than 50% within a three-year period. Any such limitation, whether as the result of our initial public offering, follow-on offerings, prior private placements, sales of our common stock by certain of our existing stockholders or additional sales of our common stock by us, may significantly reduce our ability to utilize our net operating loss carryforwards and research and development tax credit carryforwards before they expire and could have a material adverse effect on our results of operations in future years. We have performed an analysis of ownership changes through December 31, 2016 and believe that there have been changes in ownership in accordance with Section 382. However, we do not expect that these changes in ownership will materially impact our ability to utilize our net operating loss carryforwards, research and development credits or orphan drug credits, prior to their expiration, although there can be no assurance in this regard. Subsequent ownership changes, as defined by Section 382, may potentially limit the amount of net operating loss carryforwards that could be utilized to offset future taxable income. Under the TCJA, net operating carryforwards generated after December 31, 2017 will not be subject to expiration.

Healthcare legislative measures aimed at reducing healthcare costs may have a material adverse effect on our business or results of operation.

There have been, and likely will continue to be, legislation and legislative 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 unreasonable cost containment measures, drug pricing control or other reforms that do not recognize the clinical value of innovative medicines could have an adverse effect on our revenue from ZULRESSO 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, addresses 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, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% (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.

There have been a number of significant changes to the ACA and its implementation. The Tax Cuts and Jobs Act of 2017, or the TCJA, includes a provision that repealed, 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." On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. While the current Administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the Texas District Court Judge issued an order staying the judgment pending appeal, it is unclear how this decision, subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business.

On January 20, 2017, the President signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, the President signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. On June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

Moreover, on January 22, 2018, the President signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. The Bipartisan Budget Act of 2018, also amended the ACA, effective January 1, 2019, by increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and closing the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." In July 2018, CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. In addition, CMS has recently published a final rule that would give states greater flexibility, starting in 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in 2013, and, due to subsequent legislative amendments, will remain in effect through 2027 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012 further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the current administration's budget for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 legislative session, or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Additionally, the current administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The U.S. Department of HHS, has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019. Additionally, on May 10, 2019, CMS announced a new pricing transparency rule, which was to go into effect on July 9, 2019. This final rule requires direct-to-consumer television advertisements for prescription drugs and biological products for which reimbursement is available, directly or indirectly, through or under Medicare or Medicaid to include the list price of that product, except for a prescription drug or biological product that has a list price of less than $35 per month for a 30-day supply or typical course of treatment. The pricing transparency rule is being challenged in court. The pricing transparency rule could have a negative effect on our business. Congress and the current administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and 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 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. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenues at the level we expect for ZULRESSO or to commercialize any future product candidates and achieve profitability. 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 our 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 ACA, 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 any future products approved in the future, and achieve profitability.

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

Our results of operations could be adversely affected by general conditions in the U.S. and global economy and financial markets. A severe or prolonged economic downturn could result in a variety of risks to our business, including, weakened demand for our products, if any, and could adversely impact our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for any current or future approved products. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

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

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

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

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

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

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

Risks Related to Our Financial Position and Need for Capital

We are a biopharmaceutical company with a limited operating history, and have just begun to generate revenue from product sales. We have incurred significant operating losses since our inception, and anticipate that we will incur continued losses for the foreseeable future.

We are a biopharmaceutical company with a limited operating history on which investors can base an investment decision. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We were incorporated in April 2010. We have only one approved product, and only began generating revenue from product sales in the second quarter of 2019.

We have funded our operations to date primarily through proceeds from sales of common stock, redeemable convertible preferred stock and, to a lesser extent, the issuance of convertible notes. From our inception through June 30, 2019, we had received net proceeds of $2.2 billion from such transactions. As of June 30, 2019, our cash, cash equivalents and marketable securities were $1.2 billion. We have incurred significant net losses in each year since our inception, including net losses of $331.6 million for the six months ended June 30, 2019 and $372.9 million for the year ended December 31, 2018, and our accumulated deficit was $1.3 billion as of June 30, 2019. 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' deficit and working capital. We expect our research and development expenses to significantly increase in connection with clinical trials of our product candidates and efforts to seek regulatory approval for any product candidates that successfully complete clinical development. We also expect our selling, general and administrative costs to increase as we expand our operations, including in support of ongoing commercialization efforts with respect to ZULRESSO. In addition, if we obtain marketing approval for our current of future product candidates beyond ZULRESSO, we will incur significant sales, marketing and outsourced-manufacturing expenses. As a public company, we incur additional legal and accounting costs associated with operating as a public company. As a result, we expect to continue to incur 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. 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 on June 24, 2019. Our ability to generate significant product revenue from sales of ZULRESSO or any future approved product depends on a number of factors, including, but not limited to:

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

We expect to incur significant sales and marketing costs as we commercialize ZULRESSO and our product candidates, if and when successfully developed and approved. We may not be successful in our efforts to commercialize ZULRESSO or any future products. We may not achieve profitability soon after generating product sales, if ever. If we are unable to generate significant product revenue, we will not become profitable, and may be unable to continue operations without continued funding.

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

We are currently commercializing ZULRESSO and advancing our 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 and selling, general and administrative expenses to increase substantially in connection with our ongoing activities, particularly as we continue commercialization activities related to ZULRESSO, continue to advance our product candidates in clinical trials, continue our discovery efforts, seek regulatory approval of our product candidates, if we generate positive data in our other clinical programs, and commercialize other products, if successfully developed and approved. Depending on the amount and timing of revenues from sales of ZULRESSO and the status of development efforts, regulatory approval or, if approved, commercialization of our current or future product candidates, we will also require additional capital to fund operating needs. We may also need to raise additional funds if we choose to pursue additional indications and/or geographies for our product candidates, identify new potential opportunities or otherwise expand our activities more rapidly than we presently anticipate.

As of June 30, 2019, our cash, cash equivalents and marketable securities were $1.2 billion. Based on our current operating plans, we expect that our existing cash, cash equivalents and marketable securities, will be sufficient to fund our anticipated level of operations for at least the next 12 months from the filing date of this Quarterly Report. Our current operating plan does not contemplate other development activities we may pursue or that all of the currently planned activities will proceed at the same pace, or that all of the activities will be fully initiated or completed during that time. We may use available capital resources sooner than we expect under our current operating plan. In addition, our operating plan may change. We may need or choose to seek additional funds sooner than planned, through equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. In any event, we will require additional capital to expand future development efforts, obtain regulatory approval for, and to commercialize, our product candidates. Raising funds in the current economic environment may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or in light of specific strategic considerations.

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

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any 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.

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

We may seek additional capital through a combination of private and public equity offerings, debt financings, collaborations and strategic and licensing arrangements. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, the ownership interest of our stockholders in our company will be diluted. In addition, the terms of any such securities may include liquidation or other preferences that materially adversely affect the rights of our stockholders. Debt financing, if available, would increase our fixed payment obligations and may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaboration, strategic partnerships and licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates, our intellectual property, future revenue streams or grant licenses on terms that are not favorable to us.

Risks Related to Our Common Stock

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

The market price for our common stock, similar to that of other biopharmaceutical companies, is volatile. The market price of our common stock may fluctuate significantly in response to a number of factors, most of which we cannot control, including, among others:

- the results of our commercialization efforts with respect to ZULRESSO, 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 our SAGE-217 or any of our other product candidates, including positive or negative key data from such studies or clinical trials, serious adverse events arising in the course of development, or any delays or major announcements related to such studies or trials;
- announcements of new products, technologies, commercial relationships, acquisitions or other events by us or our competitors;
- the success or failure of our CNS therapies;
- regulatory or legal developments in the U.S. and other countries;
- adverse developments with respect to our intellectual property portfolio or failure to obtain or loss of exclusivity;
- failure of our future product candidates, if successfully developed and approved, to achieve commercial success;
- fluctuations in stock market prices and trading volumes of similar companies;
- general market conditions and overall fluctuations in U.S. equity markets;
- changes in healthcare laws affecting pricing, reimbursement or access;
- variations in our quarterly operating results;
- changes in our financial guidance or securities analysts’ estimates of our financial performance;
- changes in accounting principles;
- our ability to raise additional capital and the terms on which we can raise it;
- sales of large blocks of our common stock, including sales by our executive officers, directors and significant stockholders;

- additions or departures of key personnel;
- discussion of us or our stock price by the press and by online investor communities; and
- other risks and uncertainties described in these risk factors.

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

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

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

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

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

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

We do not intend to pay dividends on our common stock and, consequently, the ability of our stockholders to achieve a return on their investment will depend on appreciation in the price of our common stock.

We have never declared or paid any cash dividend on our common stock, and do not currently intend to do so in the foreseeable future. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business, and do not anticipate declaring or paying any cash dividends in the foreseeable future. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which an investor purchased them.

If equity research analysts stop publishing research or reports about our business or if they issue unfavorable commentary or downgrade our common stock, the price of our common stock could decline.

The trading market for our common stock relies in part on the research and reports that equity research analysts publish about us and our business. We do not control these analysts. The price of our common stock could decline if one or more equity research analysts downgrade our common stock or if analysts issue other unfavorable commentary or cease publishing reports about us or our business.

Item 6. Exhibits

The exhibits filed as part of this Quarterly Report are set forth on the Exhibit Index, which is incorporated herein by reference.

Exhibit Index

Exhibit No.	Description
10.1*	Eighth Amendment to Lease by and between ARE-MA Region No. 38, LLC and the Registrant, dated March 29, 2019
31.1*	Certification of Principal Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350)
31.2*	Certification of Principal Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350)
32.1+	Certification of Principal Executive Officer and Principal Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. 1350)
101.SCH*	Inline XBRL Taxonomy Extension Schema Document
101.CAL*	Inline XBRL Taxonomy Extension Calculation Document
101.LAB*	Inline XBRL Taxonomy Extension Labels Linkbase Document
101.PRE*	Inline XBRL Taxonomy Extension Presentation Link Document
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document
104	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101.*)

* Filed herewith.

\+ The certifications furnished in Exhibit 32.1 hereto are deemed to be furnished with this Quarterly Report on Form 10-Q and will not be deemed to be “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

SAGE THERAPEUTICS, INC.

August 6, 2019	By: /s/ Jeffrey M. Jonas Jeffrey M. Jonas, M.D. *Chief Executive Officer, President and Director* *(Principal Executive Officer)*
August 6, 2019	By: /s/ Kimi Iguchi Kimi Iguchi *Chief Financial Officer* *(Principal Financial and Accounting Officer)*

EIGHTH AMENDMENT TO LEASE

THIS EIGHTH AMENDMENT TO LEASE (this "**Eighth Amendment**") is made as of March 29, 2019, by and between **ARE-MA REGION NO. 38, LLC**, a Delaware limited liability company ("**Landlord**"), and **SAGE THERAPEUTICS, INC.**, a Delaware corporation ("**Tenant**").

RECITALS

A. Landlord and Tenant are now parties to that certain Lease Agreement dated as of December 21, 2011, as amended by that certain First Amendment to Lease dated as of October 26, 2012, as further amended by that certain Second Amendment to Lease dated as of May 9, 2013, as further amended by that certain Third Amendment to Lease dated as of September 9, 2015 ("**Third Amendment**"), as further amended by that certain Fourth Amendment to Lease dated as of October 27, 2015 (the "**Fourth Amendment**"), as further amended by that certain Fifth Amendment to Lease dated as of December 9, 2015, as further amended by that certain Sixth Amendment to Lease dated as of May 8, 2017, and as further amended by that certain Seventh Amendment to Lease dated as of October 23, 2018 (as amended, the "**Lease**"). Pursuant to the Lease, Tenant leases certain premises consisting of approximately 58,442 rentable square feet of space ("**Existing Premises**") in a building located at 215 First Street, Cambridge, Massachusetts ("**Building**"). The Existing Premises are more particularly described in the Lease. Capitalized terms used herein without definition shall have the meanings defined for such terms in the Lease.

B. Landlord and Tenant desire, subject to the terms and conditions set forth below, to amend the Lease to, among other things, expand the size of the Existing Premises by adding approximately 4,575 rentable square feet of space on the lower level of the Building (the "**Seventh Expansion Premises**"), as shown on **Exhibit A** attached to this Eighth Amendment.

NOW, THEREFORE, in consideration of the foregoing Recitals, which are incorporated herein by this reference, the mutual promises and conditions contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1. **<u>Seventh Expansion Premises</u>**. In addition to the Existing Premises, commencing on the Seventh Expansion Premises Commencement Date (as defined below), Landlord leases to Tenant, and Tenant leases from Landlord, the Seventh Expansion Premises.

2. **<u>Delivery</u>**. Landlord shall use reasonable efforts to deliver ("**Delivery**" or "**Deliver**") the Seventh Expansion Premises to Tenant on or before the Target Seventh Expansion Premises Commencement Date. If Landlord fails to timely Deliver the Seventh Expansion Premises, Landlord shall not be liable to Tenant for any loss or damage resulting therefrom, and the Lease with respect to the Seventh Expansion Premises shall not be void or voidable.

The "**Seventh Expansion Premises Commencement Date**" shall be the date that Landlord delivers the Seventh Expansion Premises to Tenant. The "**Seventh Expansion Premises Rent Commencement Date**" shall be the earlier of (i) the date that is 60 days after the Seventh Expansion Premises Commencement Date, or (ii) the date that Tenant commences operating its business in any portion of the Seventh Expansion Premises. The "**Target Seventh Expansion Premises Commencement Date**" shall be June 1, 2019.

Except as otherwise set forth in the Lease or this Eighth Amendment: (i) Tenant shall accept the Seventh Expansion Premises in their "as-is" condition as of the Seventh Expansion Premises Commencement Date; (ii) Landlord shall have no obligation for any defects in the Seventh Expansion Premises; and (iii) Tenant's taking possession of the Seventh Expansion Premises shall be conclusive evidence that Tenant accepts the Seventh Expansion Premises and that the Seventh Expansion Premises were in good condition at the time possession was taken. The Seventh Expansion Premises shall be delivered to Tenant without any furniture.

Upon request of Landlord, Tenant shall execute and deliver a written acknowledgment of the Seventh Expansion Premises Commencement Date and the expiration date of the Lease in a form substantially similar to the form of the "Acknowledgement of Commencement Date" attached to the Lease as **Exhibit G**; provided, however, Tenant's failure to execute and deliver such acknowledgment shall not affect Landlord's rights hereunder.

Tenant agrees and acknowledges that neither Landlord nor any agent of Landlord has made any representation or warranty with respect to the condition of all or any portion of the Seventh Expansion Premises, and/or the suitability of the Seventh Expansion Premises for the conduct of Tenant's business, and Tenant waives any implied warranty that the Seventh Expansion Premises are suitable for the Permitted Use.

3. **Definition of Premises**. Commencing on the Seventh Expansion Premises Commencement Date, the defined term "**Premises**" on Page 1 of the Lease is deleted in its entirety and replaced with the following:

"**Premises:** That portion of the Building (as defined below) containing approximately 63,017 rentable square feet, consisting of (i) approximately 5,900 rentable square feet on the second floor ("**Original Premises**"), (ii) approximately 600 rentable square feet on the second floor ("**Expansion Premises**"), (iii) approximately 4,100 rentable square feet on the second floor ("**Second Expansion Premises**"), (iv) approximately 7,962 rentable square feet on the second floor ("**Third Expansion Premises**"), (v) approximately 3,505 rentable square feet on the first floor ("**Fourth Expansion Premises**"), (vi) approximately 8,200 rentable square feet on the third floor (the "**Initial Fifth Expansion Premises**"), (vii) approximately 24,676 rentable square feet on the third floor (the "**Subsequent Fifth Expansion Premises**"), (viii) approximately 3,499 rentable square feet on the lower level (the "**Sixth Expansion Premises**"), and (ix) approximately 4,575 rentable square feet on the lower level of the Building, all as determined by Landlord, as shown on **Exhibit A**."

Exhibit A attached to the Lease is amended as of the Seventh Expansion Premises Commencement Date to include the Seventh Expansion Premises as shown on **Exhibit A** attached to this Eighth Amendment.

4. **Base Rent**.

a. **Existing Premises**. Tenant shall continue to pay Base Rent for the Existing Premises as provided for in the Lease through the Expiration Date (as defined below).

b. **Seventh Expansion Premises**. Commencing on the Seventh Expansion Premises Rent Commencement Date, Tenant shall (in addition to Base Rent for the Existing Premises) commence paying Base Rent with respect to the Seventh Expansion Premises at the rate of $41.00 per rentable square foot of the Seventh Expansion Premises per year. Commencing on each annual anniversary of the Seventh Expansion Rent Commencement Date (each, an "**Seventh Expansion Premises Adjustment Date**"), Base Rent payable with respect to Seventh Expansion Premises shall be increased by multiplying the Base Rent payable with respect to the Seventh Expansion Premises immediately before such Seventh Expansion Premises Adjustment Date by 3% and adding the resulting amount to the Base Rent payable with respect to the Seventh Expansion Premises immediately before such Seventh Expansion Premises Adjustment Date.

5. **Tenant's Share**. Commencing on the Seventh Expansion Premises Commencement Date, the defined term "**Tenant's Share**" on page 1 of the Lease is deleted in its entirety and replaced with the following:

"Tenant's Share for Original Premises and Expansion Premises: 1.77%

Tenant's Share for Second Expansion Premises: 1.12%

Tenant's Share of Third Expansion Premises: 2.17%

Tenant's Share of Fourth Expansion Premises: 0.96%

Tenant's Share of Initial Fifth Expansion Premises: 2.24%

Tenant's Share of Subsequent Fifth Expansion Premises: 6.73%

Tenant's Share of Sixth Expansion Premises: 0.95%"

Tenant's Share of Seventh Expansion Premises: 1.25%"

6. **Base Term**. Commencing on the Seventh Expansion Premises Commencement Date, the defined term "**Base Term**" on page 1 of the Lease is deleted in its entirety and replaced with the following:

"**Base Term:** Beginning (i) with respect to the Original Premises, on the Commencement Date, (ii) with respect to the Expansion Premises, on the Expansion Premises Commencement Date, (iii) with respect to the Second Expansion Premises, on the Second Expansion Premises Commencement Date, (iv) with respect to the Third Expansion Premises, on the Third Expansion Premises Commencement Date, (v) with respect to the Fourth Expansion Premises, on the Fourth Expansion Premises Commencement Date, (vi) with respect to the Initial Fifth Expansion Premises, on the Initial Fifth Expansion Premises Commencement Date, (vii) with respect to the Subsequent Fifth Expansion Premises, on the Subsequent Fifth Expansion Premises Commencement Date, (viii) with respect to the Sixth Expansion Premises on the Sixth Expansion Premises Commencement Date, and (ix) with respect to the Seventh Expansion Premises on the Seventh Expansion Premises Commencement Date, and ending with respect to the entire Premises on August 31, 2024 ("**Expiration Date**")."

7. **Rentable Area of Premises**. Commencing on the Seventh Expansion Premises Commencement Date, the defined term "**Rentable Area of Premises**" on page 1 of the Lease is deleted in its entirety and replaced with the following:

"**Rentable Area:** Approximately 63,017 square feet"

8. **Parking**. Notwithstanding anything to the contrary contained herein, commencing on the Seventh Expansion Premises Commencement Date, the number of parking spaces that Tenant is entitled to license pursuant to Section 8 of the Lease (as amended by Section 11 of the Third Amendment and Section 8 of the Fourth Amendment) shall be increased from 54 to 58 parking spaces and all references to "54" contained in Section 8 of the Lease (as amended by Section 11 of the Third Amendment and Section 8 of the Fourth Amendment) shall be deleted and replaced with "58."

For the avoidance of doubt, the parking rates payable pursuant to the Lease as of the Seventh Expansion Premises Commencement Date are equal to $325.00 per parking space per month.

9. **<u>Seventh Expansion Premises Utilities</u>**. The Seventh Expansion Premises shall be separately submetered and electricity to the Seventh Expansion Premises shall be charged directly to Tenant by Landlord. The Seventh Expansion Premises shall be subject to the terms of <u>Section 9(a)</u> of the original Lease with respect to Utilities.

10. **<u>Right to Extend Term</u>**. For the avoidance of doubt, Tenant shall continue to have the right to extend the Term of the Lease pursuant to <u>Section 34</u> of the Lease (as the same is amended by <u>Section 9</u> of the Third Amendment. Tenant may only exercise its right to extend the Term of the Lease with respect to the entire then-existing Premises.

11. **<u>Brokers</u>**. Landlord and Tenant each represents and warrants that it has not dealt with any broker, agent or other person (collectively, "**Broker**") in connection with the transaction reflected in this Eighth Amendment and that no Broker brought about this transaction, other than Cushman & Wakefield. Landlord and Tenant each hereby agrees to indemnify and hold the other harmless from and against any claims by any Broker claiming a commission or other form of compensation by virtue of having dealt with Tenant or Landlord, as applicable, with regard to this Eighth Amendment.

12. **<u>OFAC</u>**. Tenant and Landlord are currently (a) in compliance with and shall at all times during the Term of the Lease remain in compliance with the regulations of the Office of Foreign Assets Control ("**OFAC**") of the U.S. Department of Treasury and any statute, executive order, or regulation relating thereto (collectively, the "**OFAC Rules**"), (b) not listed on, and shall not during the term of the Lease be listed on, the Specially Designated Nationals and Blocked Persons List, Foreign Sanctions Evaders List or the Sectoral Sanctions Identifications List, which are all maintained by OFAC and/or on any other similar list maintained by OFAC or other governmental authority pursuant to any authorizing statute, executive order, or regulation, and (c) not a person or entity with whom a U.S. person is prohibited from conducting business under the OFAC Rules.

13. **<u>Miscellaneous</u>**.

a. This Eighth Amendment is the entire agreement between the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written agreements and discussions. This Eighth Amendment may be amended only by an agreement in writing, signed by the parties hereto.

b. This Eighth Amendment is binding upon and shall inure to the benefit of the parties hereto, their respective successors and assigns.

c. This Eighth Amendment may be executed in 2 or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature process complying with the U.S. federal ESIGN Act of 2000) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic signatures shall be deemed original signatures for purposes of this Eighth Amendment and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

d. Except as amended and/or modified by this Eighth Amendment, the Lease is hereby ratified and confirmed and all other terms of the Lease shall remain in full force and effect, unaltered and unchanged by this Eighth Amendment. In the event of any conflict between the provisions of this Eighth Amendment and the provisions of the Lease, the provisions of this Eighth Amendment shall prevail. Whether or not specifically amended by this Eighth Amendment, all of the terms and provisions of the Lease are hereby amended to the extent necessary to give effect to the purpose and intent of this Eighth Amendment.

IN WITNESS WHEREOF, the parties hereto have executed this Eighth Amendment as of the day and year first above written.

TENANT:

SAGE THERAPEUTICS, INC.,
a Delaware corporation

By: /s/ Kimi Iguchi
Its: Chief Financial Officer

LANDLORD:

ARE-MA REGION NO. 38, LLC,
a Delaware limited liability company

By: Alexandria Real Estate Equities, L.P.,
a Delaware limited partnership, managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

By: /s/ Jennifer Banks
Its: Co-Chief Operating Officer &
General Counsel

EXHIBIT A

Seventh Expansion Premises

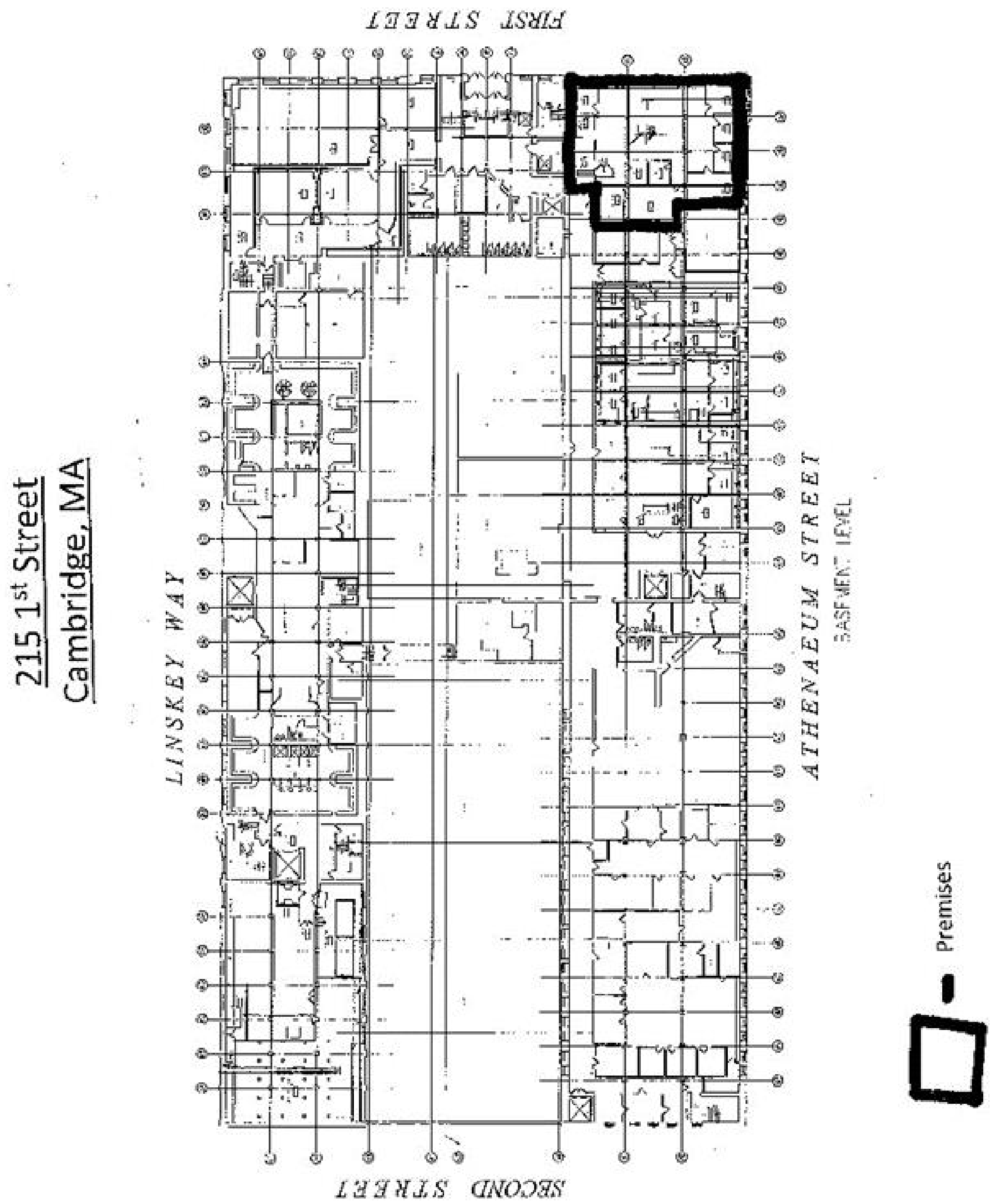


Exhibit 31.1

CERTIFICATIONS UNDER SECTION 302

I, Jeffrey M. Jonas, M.D., certify that:

1. I have reviewed this quarterly report on Form 10-Q for the period ended June 30, 2019 of Sage Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant’s other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal controls over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

(c) Evaluated the effectiveness of the registrant’s disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant’s internal control over financial reporting that occurred during the registrant’s most recent fiscal quarter (the registrant’s fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant’s internal control over financial reporting; and

5. The registrant’s other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant’s auditors and the audit committee of the registrant’s board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant’s ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant’s internal control over financial reporting.

Date: August 6, 2019

/s/ Jeffrey M. Jonas

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

Exhibit 31.2

CERTIFICATIONS UNDER SECTION 302

I, Kimi Iguchi, certify that:

1. I have reviewed this quarterly report on Form 10-Q for the period ended June 30, 2019 of Sage Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal controls over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: August 6, 2019

/s/ Kimi Iguchi

Name:	Kimi Iguchi
Title:	Chief Financial Officer (Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATIONS PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with this Quarterly Report on Form 10-Q of Sage Therapeutics, Inc. (the “Company”) for the period ended June 30, 2019, as filed with the Securities and Exchange Commission on the date hereof (the “Report”), each of the undersigned officers hereby certifies, pursuant to 18 U.S.C. (section) 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of his or her knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Jeffrey M. Jonas
Name: Jeffrey M. Jonas, M.D.
Title: Chief Executive Officer, President and Director
(Principal Executive Officer)
Date: August 6, 2019

/s/ Kimi Iguchi
Name: Kimi Iguchi
Title: Chief Financial Officer (Principal Financial and
Accounting Officer)
Date: August 6, 2019