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 September 30, 2020

OR

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

For the transition period from __________ to __________

Commission file number: 001-36544

Sage Therapeutics, Inc.
(Exact name of registrant as specified in its Charter)

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

215 First Street
Cambridge, Massachusetts 02142
(Address of principal executive 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 October 29, 2020, there were 52,044,663 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 views as to potential future results of our ongoing commercialization efforts in the U.S. with respect to ZULRESSO® (brexanolone) CIV injection, which is approved in the U.S. for the treatment of postpartum depression, or PPD;
- our planned clinical and regulatory activities with respect to zuranolone (SAGE-217) for the treatment of major depressive disorder, or MDD, and PPD and related timelines, and the potential for zuranolone in those indications and in additional indications, including our view of the potential product profile and treatment paradigm impact for zuranolone, if successfully developed and approved;
- our plans for development of our other product candidates for the treatment of central nervous system, or CNS, diseases and disorders, and potentially for other indications, and expected timelines for our planned development activities;
- our ability, within the expected time frames, to initiate clinical trials and non-clinical studies of existing or future product candidates, including pivotal clinical trials, and to successfully complete and announce the results of ongoing or future clinical trials;
- our plans and potential outcomes with respect to interactions with regulatory authorities and other research and development activities;
- our plans for and potential outcomes of 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 the level of expenses we may incur in connection with our activities; use of cash and projected cash on hand at any given timepoint; timing of future cash needs; capital requirements; sources of future financings; and our ability to obtain additional financing when needed to fund future operations;
- 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, for the indications and in the markets for which they are approved; and our ability to serve those markets;
- the potential for success of competing products that are or become available for PPD or MDD or any of the other indications that we are pursuing or may pursue in the future with our products and our product candidates;
- the potential loss of key scientific or management personnel;

- our views as to the potential impact of the COVID-19 pandemic, our efforts to address the impact of the COVID-19 pandemic and the resulting effects on our business, results of operations and activities and on any of the forward-looking statements in this Quarterly Report; 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, among other things, our industry, the general business environment, and the markets for certain diseases, including estimates regarding the potential size of those markets and the estimated incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties, and actual events, circumstances or numbers, including actual disease prevalence rates and market size, may differ materially from the information reflected in this Quarterly Report. Unless otherwise expressly stated, we obtained this industry and business information, market data, prevalence information and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties; industry, medical and general publications; government data; and similar sources, in some cases applying our own assumptions and analysis that may, in the future, prove not to have been accurate.

Sage Therapeutics, Inc.

INDEX

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)

	September 30, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 184,270	$ 126,705
Marketable securities	484,267	881,688
Prepaid expenses and other current assets	30,347	26,700
Total current assets	698,884	1,035,093
Property and equipment, net	7,404	9,126
Restricted cash	2,367	2,367
Right-of-use operating asset	26,546	33,771
Other long-term assets	3,427	3,793
Total assets	$ 738,628	$ 1,084,150
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 4,289	$ 15,266
Accrued expenses	46,756	86,618
Operating lease liability, current portion	8,620	10,244
Total current liabilities	59,665	112,128
Operating lease liability, net of current portion	21,069	26,848
Other liabilities	313	519
Total liabilities	81,047	139,495
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, $0.0001 par value per share; 5,000,000 shares authorized at September 30, 2020 and December 31, 2019; no shares issued or outstanding at September 30, 2020 and December 31, 2019	—	—
Common stock, $0.0001 par value per share; 120,000,000 shares authorized at September 30, 2020 and December 31, 2019; 52,025,862 and 51,880,227 shares issued at September 30, 2020 and December 31, 2019; 52,022,829 and 51,877,194 shares outstanding at September 30, 2020 and December 31, 2019	5	5
Treasury stock, at cost, 3,033 shares at September 30, 2020 and December 31, 2019	(400)	(400)
Additional paid-in capital	2,669,419	2,587,322
Accumulated deficit	(2,012,389)	(1,643,567)
Accumulated other comprehensive gain	946	1,295
Total stockholders' equity	657,581	944,655
Total liabilities and stockholders' equity	$ 738,628	$ 1,084,150

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 September 30,		Nine Months Ended September 30,	
	2020	2019	2020	2019
Product revenue, net	$ 1,639	$ 1,478	$ 5,014	$ 1,997
Collaboration revenue	—	2,092	—	2,911
Total revenue	1,639	3,570	5,014	4,908
Operating costs and expenses:				
Cost of goods sold	149	137	429	181
Research and development	74,078	102,108	211,008	277,565
Selling, general and administrative	35,099	88,502	143,454	260,648
Restructuring	(529)	—	27,873	—
Total operating costs and expenses	108,797	190,747	382,764	538,394
Loss from operations	(107,158)	(187,177)	(377,750)	(533,486)
Interest income, net	1,347	7,227	8,763	21,889
Other income (expense), net	76	(8)	165	12
Net loss	$ (105,735)	$ (179,958)	$ (368,822)	$ (511,585)
Net loss per share—basic and diluted	$ (2.03)	$ (3.48)	$ (7.10)	$ (10.13)
Weighted average number of common shares outstanding—basic and diluted	51,981,468	51,704,687	51,938,923	50,496,489
Comprehensive loss:				
Net loss	$ (105,735)	$ (179,958)	$ (368,822)	$ (511,585)
Other comprehensive items:				
Unrealized gain (loss) on marketable securities	(763)	202	(349)	2,292
Total other comprehensive gain (loss)	(763)	202	(349)	2,292
Total comprehensive loss	$ (106,498)	$ (179,756)	$ (369,171)	$ (509,293)

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)

	Nine Months Ended September 30, 2020	Nine Months Ended September 30, 2019
Cash flows from operating activities		
Net loss	$ (368,822)	$ (511,585)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	75,250	122,552
Premium on marketable securities	(1,066)	(2,652)
Amortization of premium (discount) on marketable securities	628	(6,429)
Depreciation	1,981	1,618
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(3,647)	(8,494)
Other long-term assets	366	(3,818)
Right-of-use operating asset	4,914	6,424
Operating lease liabilities, current	(6)	116
Operating lease liabilities, non-current	(5,194)	(6,249)
Accounts payable	(10,913)	(28,955)
Accrued expenses and other liabilities	(40,182)	25,492
Net cash used in operating activities	(346,691)	(411,980)
Cash flows from investing activities		
Proceeds from sales and maturities of marketable securities	766,339	957,840
Purchases of marketable securities	(368,829)	(1,077,702)
Purchases of property and equipment	(345)	(5,378)
Net cash provided by (used in) investing activities	397,165	(125,240)
Cash flows from financing activities		
Proceeds from stock option exercises and employee stock purchase plan issuances	7,091	46,684
Payment of employee tax obligations related to vesting of restricted stock units	—	(2,175)
Payments of offering costs	—	(328)
Proceeds from public offerings of common stock, net of commissions and underwriting discounts	—	561,277
Net cash provided by financing activities	7,091	605,458
Net increase in cash, cash equivalents and restricted cash	57,565	68,238
Cash, cash equivalents and restricted cash at beginning of period	129,072	193,310
Cash, cash equivalents and restricted cash at end of period	$ 186,637	$ 261,548
Supplemental disclosure of non-cash operating and investing activities		
Purchases of property and equipment included in accounts payable	$ —	$ 11
Right-of-use assets obtained in exchange for new operating lease liabilities	$ —	$ 872
Lease asset de-recognized upon lease cancellation	$ 2,310	$ —

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 Shares	Common Stock Amount	Treasury Stock Shares	Treasury Stock Amount	Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
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 exercises of stock options	287,659	—	—	—	14,072	—	—	14,072
Issuance of common stock under the 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 exercises 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
Issuance of common stock from exercises of stock options	248,196	—	—	—	12,436	—	—	12,436
Issuance of common stock under the employee stock purchase plan	39,006	—	—	—	3,946	—	—	3,946
Stock-based compensation expense	—	—	—	—	43,053	—	—	43,053
Unrealized gain on available-for-sale securities	—	—	—	—	—	202	—	202
Vesting of restricted stock units, net of employee tax obligations	59,686	—	—	—	(1,483)	—	—	(1,483)
Net loss	—	—	—	—	—	—	(179,958)	(179,958)
Balances at September 30, 2019	51,815,992	$ 5	3,033	$ (400)	$ 2,554,603	$ 1,777	$ (1,474,914)	$ 1,081,071
Balances at December 31, 2019	51,877,194	$ 5	3,033	$ (400)	$ 2,587,322	$ 1,295	$ (1,643,567)	$ 944,655
Issuance of common stock from exercises of stock options	7,196	—	—	—	367	—	—	367
Issuance of common stock under the employee stock purchase plan	33,429	—	—	—	2,793	—	—	2,793
Stock-based compensation expense	—	—	—	—	30,218	—	—	30,218
Unrealized loss on available-for-sale securities	—	—	—	—	—	(2,087)	—	(2,087)
Net loss	—	—	—	—	—	—	(126,740)	(126,740)
Balances at March 31, 2020	51,917,819	$ 5	3,033	$ (400)	$ 2,620,700	$ (792)	$ (1,770,307)	$ 849,206
Issuance of common stock from exercises of stock options	17,160	—	—	—	387	—	—	387
Stock-based compensation expense	—	—	—	—	24,168	—	—	24,168
Unrealized gain on available-for-sale securities	—	—	—	—	—	2,501	—	2,501
Net loss	—	—	—	—	—	—	(136,347)	(136,347)
Balances at June 30, 2020	51,934,979	$ 5	3,033	$ (400)	$ 2,645,255	$ 1,709	$ (1,906,654)	$ 739,915
Issuance of common stock from exercises of stock options	48,560	—	—	—	2,157	—	—	2,157
Issuance of common stock under the employee stock purchase plan	39,290	—	—	—	2,144	—	—	2,144
Stock-based compensation expense	—	—	—	—	19,863	—	—	19,863
Unrealized loss on available-for-sale securities	—	—	—	—	—	(763)	—	(763)
Net loss	—	—	—	—	—	—	(105,735)	(105,735)
Balances at September 30, 2020	52,022,829	$ 5	3,033	$ (400)	$ 2,669,419	$ 946	$ (2,012,389)	$ 657,581

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 first product, ZULRESSO® (brexanolone) CIV 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 central nervous system (“CNS”) receptor systems, GABA and NMDA. The GABA receptor family, which is recognized as the major inhibitory neurotransmitter in the CNS, mediates downstream neurologic and bodily function via activation of 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 biotechnology and pharmaceutical industries, including, but not limited to, the risks associated with developing product candidates at each stage of non-clinical and clinical development; the challenges associated with gaining regulatory approval of such product candidates; the risks associated with the marketing and sale of pharmaceutical products; the potential for development by third parties of new technological innovations that may compete with the Company’s products and product candidates; the dependence on key personnel; the challenges of protecting proprietary technology; the need to comply with government regulations; the high costs of drug development; the impact of the COVID-19 pandemic on its operations and financial condition; and the uncertainty of being able to secure additional capital when needed to fund operations.

Under Accounting Standards Update (“ASU”) No. 2014-15, *Presentation of Financial Statements—Going Concern* (Subtopic 205-40) (“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 September 30, 2020, the Company had an accumulated deficit of $2.0 billion. From its inception through September 30, 2020, the Company has received aggregate net proceeds of $2.2 billion from the sales of redeemable convertible preferred stock prior to its initial public offering, 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. 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 or other sources of funding when needed, the Company may be required to delay, limit, reduce or terminate product development or future commercialization efforts or grant rights to develop and market products or product candidates that the Company would otherwise prefer to develop and market itself.

The Company expects that, based on its current operating plans, the Company’s existing cash, cash equivalents and marketable securities will be sufficient to fund its current planned operations for at least the next twelve months from the issuance of these unaudited interim condensed consolidated financial statements (“condensed consolidated financial statements”). At some point after that time, the Company will require additional financing to fund its future operations. Even if the Company believes it has sufficient funds for its current or future operating plans, the Company may seek to raise additional capital if market conditions are favorable or in light of other strategic considerations.

COVID-19

The ongoing COVID-19 pandemic has caused and may continue to cause major disruptions to businesses and financial markets worldwide. The rapid spread of COVID-19 in the U.S. has resulted in a significant reduction in patient demand for ZULRESSO and in the number of sites available to administer ZULRESSO. This has had a negative impact on the Company's revenue from sales of ZULRESSO. While there have been no material disruptions to date, any prolonged material disruptions to the work of the Company's employees, suppliers, contract manufacturers, or vendors as a result of the COVID-19 pandemic could negatively impact the Company's activities, availability of supplies, or operating results. Similarly, while to date the Company has not experienced significant impacts to the Company's development activities, any material disruption to the Company's development activities as a result of the COVID-19 pandemic may cause delays, increase the Company's costs and impact the Company's operating results. In addition, the COVID-19 pandemic has caused major volatility in capital markets and a significant global economic downturn, and the Company's ability to access the capital markets in the future could be negatively impacted if volatility in the capital markets and the economic downturn continue.

2. Summary of Significant Accounting Policies

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

Basis of Presentation

The 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 condensed consolidated financial statements should be read in conjunction with the audited consolidated financial statements as of and for the year ended December 31, 2019, included in the Company's Annual Report on Form 10-K for the year ended December 31, 2019.

The 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 condensed consolidated financial statements contain all adjustments, consisting of only normal recurring adjustments, necessary for a fair statement of its financial position as of September 30, 2020, its results of operations and comprehensive loss for the three and nine months ended September 30, 2020 and 2019, its cash flows for the nine months ended September 30, 2020 and 2019, and its statements of changes in stockholders' equity for the three and nine months ended September 30, 2020 and 2019. The consolidated balance sheet at December 31, 2019 was derived from audited financial statements, but does not include all disclosures required by GAAP. The results for the three and nine months ended September 30, 2020 are not necessarily indicative of the results for the year ending December 31, 2020, or for any future period.

Principles of Consolidation

The 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, 2019. Intercompany accounts and transactions have been eliminated.

Use of Estimates

The preparation of condensed 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 condensed consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. The full extent to which the COVID-19 pandemic will directly or indirectly impact the Company's business, results of operations and financial condition, including sales, expenses, reserves and allowances, manufacturing, clinical trials, research and development costs and employee-related amounts, will depend on future developments that are highly uncertain, including developments related to the scope and duration of the pandemic; the timing, extent and frequency of surges in the number of cases of COVID-19; new information that may emerge concerning COVID-19; and the actions taken to contain the COVID-19 pandemic. The Company has made estimates of the impact of the COVID-19 pandemic within its consolidated financial statements, and there may be changes to those estimates in future periods. Actual results could differ from those estimates.

Research and Development Costs and Accruals

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

The Company has entered into various research and development contracts with research institutions and other companies both inside and outside of the U.S. These agreements are generally cancelable, and related costs are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing research and development costs. When billing terms under these contracts do not coincide with the timing of when the work is performed, the Company is required to make estimates of outstanding obligations to those third parties as of the end of the reporting period. Any accrual estimates are based on a number of factors, including the Company's knowledge of the progress towards completion of the research and development activities, invoicing to date under the contracts, communication from the research institution or other companies of any actual costs incurred during the period that have not yet been invoiced, and the costs included in the contracts. Significant judgments and estimates 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 units, made to employees and non-employee directors based on the estimated fair value on the date of grant, over the requisite service period. The Company recognizes stock-based compensation expense for only the portion of awards that are expected to vest.

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

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 expected to continue to do so until such time as it has adequate historical data regarding the volatility of its common stock price for the duration of the expected term. Effective January 1, 2020, the Company began using the historical volatility of only its common stock, as there is adequate historical data for the duration of the expected term.

The expected term of the 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 the options granted to non-employee consultants was determined based on the contractual term of the options, and since January 1, 2019, the "simplified" method has been 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.

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 September 30, 2020, cash equivalents were comprised of money market funds. As of December 31, 2019, cash equivalents were comprised of commercial paper 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 marketable securities to be available-for-sale. Accordingly, these investments are recorded at fair value, which is based on quoted market prices. Unrealized gains and losses are reported as the accumulated other comprehensive items in stockholders' equity. When the fair value is below the amortized cost of the asset, an estimate of expected credit losses is made. The credit-related impairment amount is recognized in net income; the remaining impairment amount and unrealized gains are reported as a component of accumulated other comprehensive income (loss) in stockholders' equity. Credit losses are recognized through the use of an allowance for credit losses account and subsequent improvements in expected credit losses are recognized as a reversal of an amount in the allowance account. If the Company has the intent to sell the security or it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis, then the allowance for the credit loss is written-off and the excess of the amortized cost basis of the asset over its fair value is recorded in net income.

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 September 30, 2020 and December 31, 2019 were carried at fair value, determined according to the fair value hierarchy; see Note 3, Fair Value Measurements.

The carrying amounts reflected in the condensed consolidated balance sheets for accounts payable and accrued expenses approximate their fair values due to their short-term maturities at September 30, 2020 and December 31, 2019, respectively.

Revenue Recognition

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 and supply agreement with Shionogi & Co., Ltd. ("Shionogi"). The terms of the Company's collaboration agreement include consideration such as non-refundable license fees, reimbursement of any development costs the Company incurs on behalf of Shionogi, payments due upon the achievement, if any, of clinical and pre-clinical performance-based development milestones, regulatory milestones, and sales-based milestones and royalties on product sales, if development is successful in the Shionogi territory, as well as payments for the supply of active pharmaceutical ingredient ("API") and drug product for clinical trials. To date, revenue from the Company's collaboration agreement with Shionogi has come from an initial, upfront license fee upon execution of the agreement and from the supply of API for Shionogi's clinical trials.

Under Accounting Standards Codification ("ASC") Topic 606, "*Revenue from Contracts with Customers*" ("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. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. The Company assesses if these options provide a material right to the customer and if so, they are considered performance obligations. The exercise of a material right may be accounted for as a contract modification or as a continuation of the contract for accounting purposes. For contracts determined to be within the scope of Topic 606, the Company assesses whether the goods or services promised within each contract are distinct to identify those that are performance obligations. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract. The Company allocates the transaction price (the amount of consideration it expects to be entitled to from a customer in exchange for the promised goods or services) to each performance obligation and recognizes the associated revenue when (or as) each performance obligation is satisfied. The Company's estimate of the transaction price for each contract includes all variable consideration to which the Company expects to be entitled.

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 condensed consolidated financial statements at the point in time when control transfers to the customer, which is typically when the product has been delivered to the customer's location. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. The Company's only performance obligation identified for ZULRESSO is to deliver the product to the location specified by the customer's order. The Company records shipping and handling costs associated with delivery of product to its customers within selling, general and administrative expenses on its condensed 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 September 30, 2020, as customer invoicing generally occurs before or at the time of revenue recognition. The Company did not have any contract liabilities at September 30, 2020, 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 condensed consolidated balance sheets.

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

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 condensed consolidated statements of operations and comprehensive loss. Inventory is included in prepaid expenses and other current assets on the condensed consolidated balance sheets and the amount was not significant as of September 30, 2020.

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 condensed 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 three and nine months ended September 30, 2020 and 2019.

Accounts Receivable

The Company's trade accounts receivable consist of amounts due from specialty distributors, specialty pharmacies and medically-supervised healthcare settings that have been certified under a Risk Evaluation and Mitigation Strategy ("REMS") program in the U.S. related to sales of ZULRESSO and have standard payment terms that generally require payment within 30 to 90 days from the invoice date. The Company monitors the financial performance and creditworthiness of customers so that it can properly assess and respond to changes in their credit 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 condensed consolidated balance sheets. As of September 30, 2020, the Company has not provided any allowance for bad debts against the trade accounts receivable, and the amount of trade accounts receivable was not significant.

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 the right-of-use operating asset; operating lease liability, current portion; and operating lease 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.

Variable lease payments are the amounts owed by the Company to a lessor that are not fixed, such as reimbursement for common area maintenance and utilities costs for facility leases and maintenance and tolls for leased vehicles. Variable lease payments are expensed when incurred.

Recently Issued Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board ("FASB") issued ASU No. 2016-02, *Leases (Topic 842)*, which replaced the existing guidance in ASC 840, "Leases". The FASB subsequently issued the following amendments to ASU No. 2016-02 that have the same effective date and transition date: ASU No. 2018-01, *Leases (Topic 842): Land Easement Practical Expedient for Transition to Topic 842*; ASU No. 2018-10, *Codification Improvements to Topic 842, Leases*; ASU No. 2018-11, *Leases (Topic 842): Targeted Improvements*; ASU No. 2018-20, *Narrow-Scope Improvement for Lessors*; and ASU No. 2019-01, *Leases (Topic 842): Codification Improvements*. The Company adopted these amendments with ASU No. 2016-02 effective January 1, 2019 (ASU No. 2016-02 as amended, "ASC 842"). The ASC 842 standard generally requires lessees to recognize operating and financing lease liabilities and corresponding right-of-use assets on the condensed consolidated balance sheets 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 condensed consolidated statements of operations and comprehensive loss and condensed 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 condensed consolidated balance sheets and will recognize the associated lease payments in the condensed consolidated statements of operations and comprehensive loss on a straight-line basis over the lease term. On the adoption 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 condensed 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*. This standard amends the impairment model by requiring entities to use a forward-looking approach based on expected losses to estimate credit losses for most financial assets and certain other instruments that are not measured at fair value through net income. For available-for-sale debt securities, entities are required to recognize an allowance for credit losses rather than a reduction in carrying value of the asset. Entities are no longer permitted to consider the length of time that fair value has been less than amortized cost when evaluating when credit losses should be recognized. The Company adopted the standard on the required effective date of January 1, 2020, on a prospective basis. This guidance did not have a significant impact on the Company's condensed consolidated financial statements and related disclosures.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework - Changes to the Disclosure Requirements for Fair Value Measurement*. This standard modifies certain disclosure requirements on fair value measurements. The Company adopted the standard on the required effective date of January 1, 2020. This guidance did not have a significant impact on the Company's condensed consolidated financial statements and related disclosures.

In December 2019, the FASB issued ASU No. 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes.* This standard enhances and simplifies various aspects of the income tax accounting guidance in ASC 740, including requirements related to hybrid tax regimes, the tax basis step-up in goodwill obtained in a transaction that is not a business combination, separate financial statements of entities not subject to tax, the intra-period tax allocation exception to the incremental approach, ownership changes in investments, changes from a subsidiary to an equity method investment, interim-period accounting for enacted changes in tax law, and the year-to-date loss limitation in interim-period tax accounting. This guidance will be effective for the Company for annual and interim periods beginning after December 31, 2020; however, early adoption is permitted. The Company is currently in the process of evaluating the impact to its consolidated financial statements.

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

3. Fair Value Measurements

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

The fair values of the Company's marketable securities are based on prices obtained from independent pricing sources. Consistent with the fair value hierarchy described in Note 2, Summary of Significant Accounting Policies, 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 cash equivalents and marketable securities as of September 30, 2020 and December 31, 2019.

	September 30, 2020			
	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	$ 184,270	$ 184,270	$ —	$ —
Total cash equivalents	184,270	184,270	—	—
Marketable securities:				
U.S. government securities	172,742	—	172,742	—
U.S. corporate bonds	174,964	—	174,964	—
International corporate bonds	65,682	—	65,682	—
U.S. commercial paper	40,947	—	40,947	—
International commercial paper	29,932	—	29,932	—
Total marketable securities	484,267	—	484,267	—
	$ 668,537	$ 184,270	$ 484,267	$ —

	December 31, 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	$ 126,705	$ 65,414	$ 61,291	$ —
Total cash equivalents	126,705	65,414	61,291	—
Marketable securities:				
U.S. government securities	205,328	—	205,328	—
U.S. corporate bonds	429,845	—	429,845	—
International corporate bonds	142,998	—	142,998	—
U.S. commercial paper	52,261	—	52,261	—
International commercial paper	51,256	—	51,256	—
Total marketable securities	881,688	—	881,688	—
	$ 1,008,393	$ 65,414	$ 942,979	$ —

During the nine months ended September 30, 2020 and 2019, 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 September 30, 2020 and December 31, 2019:

	September 30, 2020				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
	(in thousands)				
Assets:					
U.S. government securities	$ 172,685	$ 72	$ (15)	$ —	$ 172,742
U.S. corporate bonds	174,465	514	(15)	—	174,964
International corporate bonds	65,291	391	—	—	65,682
U.S. commercial paper	40,948	1	(2)	—	40,947
International commercial paper	29,932	—	—	—	29,932
	$ 483,321	$ 978	$ (32)	$ —	$ 484,267

	December 31, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in thousands)			
Assets:				
U.S. government securities	$ 205,172	$ 176	$ (20)	$ 205,328
U.S. corporate bonds	429,148	797	(100)	429,845
International corporate bonds	142,568	457	(27)	142,998
U.S. commercial paper	52,252	14	(5)	52,261
International commercial paper	51,253	5	(2)	51,256
	$ 880,393	$ 1,449	$ (154)	$ 881,688

As of September 30, 2020, all marketable securities held by the Company had remaining contractual maturities of one year or less, except for corporate bonds with a fair value of $18.9 million, that had maturities of one to two years. As of December 31, 2019, all marketable securities held by the Company had remaining contractual maturities of one year or less, except for corporate bonds with a fair value of $137.1 million, that had maturities of one to two years.

As of September 30, 2020, the marketable securities in a loss position had a maturity of less than one year, except for corporate bonds with a fair value of $4.0 million, that had maturities of one to two years. As of December 31, 2019, the marketable securities in a loss position had a maturity of less than one year.

There have been no impairments of the Company's assets measured and carried at fair value during the nine months ended September 30, 2020 and the year ended December 31, 2019.

4. Balance Sheet Components

Property and Equipment, net

Property and equipment, net, consists of the following:

	September 30, 2020	December 31, 2019
	(in thousands)	
Computer hardware and software	$ 2,758	$ 2,830
Furniture and equipment	1,865	1,828
Leasehold improvements	9,220	8,967
	13,843	13,625
Less: Accumulated depreciation	(6,439)	(4,499)
	$ 7,404	$ 9,126

Depreciation expense for the three months ended September 30, 2020 and 2019 was $0.7 million and $0.7 million, respectively. Depreciation expense for the nine months ended September 30, 2020 and 2019 was $2.0 million and $1.6 million, respectively.

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

Accrued Expenses

Accrued expenses consist of the following:

	September 30, 2020	December 31, 2019
	(in thousands)	
Accrued research and development costs	$ 29,233	$ 46,940
Restructuring	1,356	-
Employee-related	9,147	22,011
Professional services	6,045	16,720
Other	975	947
	$ 46,756	$ 86,618

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 condensed consolidated balance sheets 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. 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.

From June 2018 to January 2019, the Company entered into leases for vehicles for field-based employees. These leases were determined to be operating leases and a right-of-use operating asset in the amount of $5.3 million was recorded on the balance sheet upon implementation of the new lease standard on January 1, 2019. The leases were for a term of three years and were to expire on various dates through January 31, 2022. During the three months ended June 30, 2020, these leases were terminated as part of the restructuring (see Note 10, Restructuring), and the remaining asset of $2.3 million and the liabilities related to these leases were de-recognized upon termination of the leases.

As of January 1, 2019, the Company leased office space in two multi-tenant buildings in Cambridge, Massachusetts, consisting of 58,442 square feet in the first building under an operating lease that will expire on August 15, 2024, 40,419 square feet in the second building under an operating lease that will expire on August 31, 2024; and in a multi-tenant building in Raleigh, North Carolina, consisting of 15,525 square feet under an operating lease that will expire on November 30, 2024.

In December 2018, the Company entered into a lease for office space in a third multi-tenant building in Cambridge, Massachusetts. The amount of square feet of office space is 15,975 square feet and the lease period began on March 1, 2019. The term for this lease will expire on February 29, 2024.

In March 2019, the Company entered into the Eighth Amendment to the lease for office space in the first multi-tenant 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 Pharmaceuticals, Inc. ("CyDex"), a wholly owned subsidiary of Ligand Pharmaceuticals, Inc., 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 such product candidate is successfully developed in the future. Royalty rates are in the low single digits based on levels of net sales. As of September 30, 2020, the Company has paid to CyDex $1.0 million for licensing fees, which was recorded as research and development expense.

Under the amended and restated license agreement with CyDex, the Company agreed to make milestone payments on the achievement of clinical development and regulatory milestones in the amount of up to $0.8 million in clinical milestones and up to $3.8 million in regulatory milestones for each of the first two fields with respect to brexanolone; up to $1.3 million in clinical milestones and up to $8.5 million in regulatory milestones for each of the third and fourth fields with respect to brexanolone; and up to $0.8 million in clinical milestones and up to $1.8 million in regulatory milestones for one field with respect to SAGE-689. As of September 30, 2020, 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 related to these regulatory milestones.

For the three and nine months ended September 30, 2020, and the three months ended September 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 or SAGE-689 under the license agreement with CyDex. For the nine months ended September 30, 2019, the Company recorded an intangible asset of $3.0 million related to a regulatory milestone for the brexanolone program under the license agreement with CyDex.

As of September 30, 2020, the Company has made no milestone payments related to clinical development or regulatory milestones for SAGE-689 under the license agreement with CyDex.

University of California License Agreements

In October 2013, the Company entered into a non-exclusive license agreement with The Regents of the University of California under which the Company was granted a non-exclusive license to certain clinical data and clinical material related to brexanolone for use in the development and commercialization of biopharmaceutical products in the licensed field, including status epilepticus and postpartum depression. In May 2014, the license agreement was amended to add the treatment of essential tremor to the licensed field of use, materials and milestone fee provisions of the agreement. The Company paid to The Regents of the University of California clinical development milestones of $0.1 million, prior to December 31, 2015; no other milestones are outstanding under this non-exclusive license agreement. The Company is required to pay royalties of less than 1% on net sales for a period of fifteen years following the sale of the first product developed using the data and materials. 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 September 30, 2020, 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 and nine months ended September 30, 2020, and the three months ended September 30, 2019, the Company did not record any expense or make any milestone payments under the license agreements with The Regents of the University of California. For the nine months ended September 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.

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 September 30, 2020, the Company has recorded research and development expense and made a cash payment of $50,000 related to these clinical 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 nine months ended September 30, 2020 and 2019, the Company did not record any expense or make any milestone payments under the license agreement with Washington University.

6. Collaboration Agreement

Effective June 12, 2018, the Company entered into a strategic collaboration with Shionogi for the clinical development and commercialization of zuranolone for the treatment of major depressive disorder ("MDD") and other potential indications in Japan, Taiwan and South Korea. On October 26, 2018, the Company entered into a supply agreement with Shionogi for zuranolone clinical material.

Under the terms of the collaboration agreement, Shionogi will be responsible for all clinical development, regulatory filings and commercialization of zuranolone 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. The Company is eligible to receive tiered royalties on sales of zuranolone 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 zuranolone in Japan. The Company maintains exclusive rights to develop and commercialize zuranolone outside of Japan, Taiwan and South Korea. The upfront cash payment and any payments for milestones and royalties are non-refundable and non-creditable. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any milestone payments or any royalty payments from Shionogi.

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

In determining the appropriate amount of revenue to be recognized under Topic 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 satisfied each performance obligation.

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

Under the clinical supply agreement, the Company will manufacture and supply to Shionogi (i) clinical quantities of API reasonably required by Shionogi for the development of licensed products in the Shionogi territory under the collaboration and license agreement and (ii) quantities of drug product reasonably required for use by Shionogi in Phase 1 studies of zuranolone in the Shionogi territory under the collaboration and license agreement, in the quantities agreed to by the parties. Collaboration revenue from the clinical supply agreement, which excludes the $90.0 million upfront payment, pertains to the clinical material sold under the terms of the clinical supply agreement. The Company records the costs related to the clinical supply agreement in research and development expense on its condensed consolidated statements of operations and comprehensive loss.

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, which was in the three months ended June 30, 2018. The remaining transaction price related to the performance obligation for the supply of certain clinical material is not significant. The potential milestone payments that the Company is eligible to receive were excluded from the transaction price, as all milestone amounts were fully constrained based on the probability of achievement. The Company will re-evaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, and, if necessary, adjust its estimate of the transaction price.

7. Sale of Equity Securities

On February 27, 2019, the Company completed the sale of 3,833,334 shares of its common stock in a follow-on 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

Equity Plans

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

The 2014 Plan provides for an annual increase, to be added on the first day of each fiscal year, by up to 4% of the Company’s outstanding shares of common stock as of the last day of the prior year. On January 1, 2020, 2,075,087 shares of common stock, representing 4% of the Company’s outstanding shares of common stock as of December 31, 2019, were added to the 2014 Plan.

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

As of September 30, 2020, the total number of shares reserved under all equity plans was 12,580,983 and the total number of shares available for future issuance under all equity plans was 4,264,646 shares

Restricted Stock Units

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

	Shares
Outstanding as of December 31, 2019	333,243
Granted	995,506
Vested	—
Forfeited	(341,753)
Outstanding as of September 30, 2020	986,996

During the three months ended March 31, 2017, the Company granted 32,500 time-based restricted stock units to certain employees of the Company. The Company did not grant time-based restricted stock units prior to January 1, 2017. These time-based restricted stock units vested ratably over two years, with 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. The fair value of the time-based restricted stock units that vested during the nine months ended September 30, 2019 was $2.0 million.

No time-based restricted stock units vested during the three and nine months ended September 30, 2020 and the three months ended September 30, 2019.

During the nine months ended September 30, 2020, the Company granted 550,890 time-based restricted stock units to certain employees of the Company. These time-based restricted stock units will vest over two years, with 25% vesting at the one-year anniversary of the grant date and 75% vesting at the two-year anniversary of the grant date, which will be in April 2021 and April 2022, respectively. During the three months ended September 30, 2020, the Company granted no time-based restricted stock units.

During the year ended December 31, 2018, the Company granted 37,800 performance restricted stock units that will vest upon the achievement of a certain commercial milestone.

During the three months ended September 30, 2020 and 2019, the Company granted to employees of the Company 11,800 and 16,258 performance restricted stock units, respectively; and during the nine months ended September 30, 2020 and 2019, the Company granted 444,616 and 386,714 performance restricted stock units, respectively. These performance restricted stock units are related to the achievement of certain clinical and regulatory development milestones related to product candidates and commercial milestones.

Recognition of stock-based compensation expense associated with performance restricted stock units commences when the performance condition is considered probable of achievement, using management's best estimates, which consider the inherent risk and uncertainty regarding the future outcomes of the milestones.

During the three months ended September 30, 2019, one milestone for a performance restricted stock unit was achieved. This milestone represents 18% of the performance restricted stock units that were granted during the nine months ended September 30, 2019. The fair value of the performance restricted stock units that vested during the three and nine months ended September 30, 2019 was $11.1 million.

No performance restricted stock units vested during the three and nine months ended September 30, 2020.

At September 30, 2020, 986,996 restricted stock units were both outstanding and unvested, and the total unrecognized stock-based compensation expense related to those awards was $61.4 million.

Option Rollforward

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

	Shares	Weighted Average Exercise Price	Weighted Average Remaining Life (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2019	8,163,113	$ 106.30	7.75	$ 87,972
Granted	1,443,795	$ 55.23		
Exercised	(72,916)	$ 39.91		
Forfeited	(2,204,651)	$ 120.69		
Outstanding as of September 30, 2020	7,329,341	$ 92.58	7.14	$ 69,947
Exercisable as of September 30, 2020	4,500,068	$ 88.63	6.25	$ 53,983

At September 30, 2020, the Company had unrecognized stock-based compensation expense related to its unvested service-based stock option awards of $143.3 million, which is expected to be recognized over the remaining weighted average vesting period of 1.83 years.

The intrinsic value of stock options exercised during the nine months ended September 30, 2020 and 2019 was $0.9 million and $115.2 million, respectively.

Performance-Based Stock Options

Since January 1, 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 unmet commercial milestone that was 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. During the three months ended June 30, 2019, this commercial milestone was achieved. Stock options with this milestone were granted during the years ended December 31, 2018 and 2017. 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 nine months ended September 30, 2019, the Company recognized stock-based compensation expense related to this milestone of $16.3 million.

As of September 30, 2020 and 2019, for performance-based option 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 has been recognized related to these awards in the nine months ended September 30, 2020 and 2019.

As of September 30, 2020, 383,906 performance-based stock options were both outstanding and unvested, and the total unrecognized stock-based compensation expense related to those awards was $29.0 million.

Stock-Based Compensation Expense

Stock-based compensation expense recognized during the three and nine months ended September 30, 2020 and 2019 was as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2020	2019	2020	2019
	(in thousands)			
Research and development	$ 9,927	$ 17,111	$ 32,270	$ 51,528
Selling, general and administrative	10,181	26,558	41,192	71,024
Restructuring	—	—	1,788	—
	$ 20,108	$ 43,669	$ 75,250	$ 122,552

Stock-based compensation expense recognized during the three and nine months ended September 30, 2020 and 2019 by award type was as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2020	2019	2020	2019
	(in thousands)			
Stock options	$ 18,797	$ 32,119	$ 72,434	$ 109,963
Restricted stock units	1,066	10,934	1,815	10,992
Employee stock purchase plan	245	616	1,001	1,597
	$ 20,108	$ 43,669	$ 75,250	$ 122,552

The stock-based compensation expense recorded for the restructuring in the nine months ended September 30, 2020 is the incremental amount related to modifying the exercise period for outstanding, vested option grants that had been made to employees who were terminated in the restructuring.

The weighted average grant date fair value per share of stock options granted under the Company’s stock option plans during the nine months ended September 30, 2020 and 2019 was $37.04 and $99.49, respectively.

9. Net Loss Per Share

Basic and diluted net loss per share was calculated as follows for the three and nine months ended September 30, 2020 and 2019:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2020	2019	2020	2019
Basic net loss per share:				
Numerator:				
Net loss (in thousands)	$ (105,735)	$ (179,958)	$ (368,822)	$ (511,585)
Denominator:				
Weighted average common stock outstanding —basic	51,981,468	51,704,687	51,938,923	50,496,489
Dilutive effect of shares of common stock equivalents resulting from common stock options and restricted stock units	—	—	—	—
Weighted average common stock outstanding —diluted	51,981,468	51,704,687	51,938,923	50,496,489
Net loss per share—basic and diluted	$ (2.03)	$ (3.48)	$ (7.10)	$ (10.13)

The following common stock equivalents outstanding as of September 30, 2020 and 2019 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 September 30,		Nine Months Ended September 30,	
	2020	2019	2020	2019
Stock options	6,945,435	7,085,322	6,945,435	7,085,322
Restricted stock units	489,495	—	489,495	—
Employee stock purchase plan	16,396	10,900	16,396	10,900
	7,451,326	7,096,222	7,451,326	7,096,222

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.

10. Restructuring

In April 2020, the Company announced a restructuring plan to enable the Company to advance its corporate strategy and pipeline that included the elimination of approximately 53% of the Company's workforce. The workforce reduction primarily affected the ZULRESSO commercial operation and related selling, general and administrative support functions. In the nine months ended September 30, 2020, the Company recorded $27.9 million of expense, primarily for one-time termination benefits to the affected employees, primarily for cash payments of severance, healthcare benefits and outplacement assistance.

The Company expects that substantially all of the accrued restructuring charges as of September 30, 2020 will be paid in cash by the end of 2020. Restructuring activity during the nine months ended September 30, 2020 was as follows:

	Restructuring accrual (in thousands)
Balance as of January 1, 2020	$ -
Restructuring expenses incurred	27,873
Cash paid	(24,079)
Non-cash activity	(2,438)
Balance as of September 30, 2020	$ 1,356

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 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, 2019, 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, as such statements speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the Securities and Exchange Commission, or SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

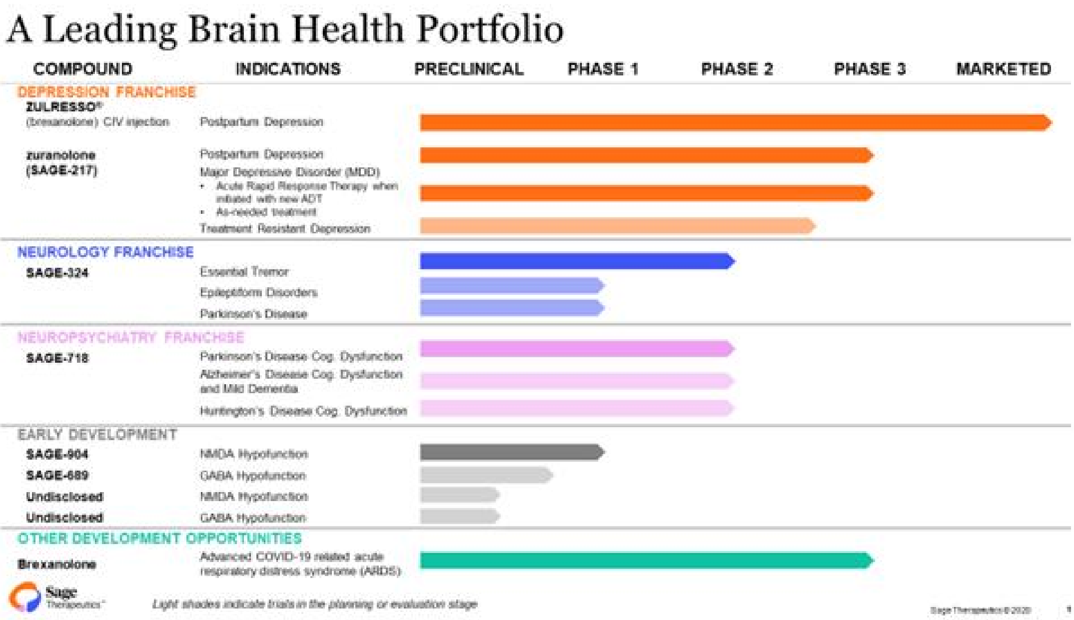
Overview

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 first product, ZULRESSO® (brexanolone) CIV 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. We have a portfolio of other product candidates with a current focus on modulating two critical central nervous system, or CNS, receptor systems, GABA and NMDA. The GABA receptor family, which is recognized as the major inhibitory neurotransmitter in the CNS, mediates downstream neurologic and bodily function via activation of 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 COVID-19 pandemic has caused and may continue to cause major disruptions to businesses and financial markets worldwide. The pandemic continues to significantly impact the U.S. Given the rapid development and continued fluidity of the COVID-19 pandemic, we cannot predict its course or for how long and to what extent it will continue to have a negative impact in the U.S. and worldwide. We are closely monitoring the impact of the pandemic on our employees, and our business operations. We have adopted a series of precautionary measures in an effort to protect our employees and mitigate the potential spread of COVID-19 in our community. For example, we have instituted a remote work policy for our employees, including our field-based employees, and have temporarily replaced all in-person meetings and interactions with virtual interactions.

The rapid spread of COVID-19 in the U.S. has resulted in a significant reduction in patient demand for ZULRESSO and in the number of sites available to administer ZULRESSO. This has had a negative impact on our revenue from sales of ZULRESSO. The COVID-19 pandemic may also negatively impact our ongoing and planned development activities. While to date we have not experienced significant impacts to our development activities, concerns, precautions and restrictions arising from the COVID-19 pandemic may substantially slow clinical site recruitment and initiation; impede enrollment; impair the conduct, auditing, monitoring, or completion of our trials; impair or impede the timeliness and completion of our data collection and analysis efforts or the integrity of our data; or cause us to pause trials. Any of these effects may significantly impact our ability to meet our expected timelines or increase our costs, impact other aspects of our business, or cause us to have to change our plans. To date, we and our third-party suppliers and contract manufacturing partners have been able to continue to supply ZULRESSO and our product candidates without significant disruption, and we currently do not anticipate any interruptions in supply. Any prolonged material disruptions to the work of our employees, suppliers, contract manufacturers, or vendors as a result of the COVID-19 pandemic could negatively impact our business, results of operations, and activities. In addition, the COVID-19 pandemic has caused major volatility in capital markets and a significant global economic downturn, and the Company's ability to access the capital markets in the future could be negatively impacted if volatility in the capital markets and the economic downturn continue.

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



Our first product, ZULRESSO, 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 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. PPD is one of the most common medical complications during and after pregnancy.

ZULRESSO is administered as a continuous infusion given over two and a half days. Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness during the ZULRESSO infusion, ZULRESSO is approved for administration only in a medically-supervised healthcare setting that has been certified under a Risk Evaluation and Mitigation Strategy, or REMS, program and meets the other requirements of the REMS program, including requirements related to monitoring of the patient during the infusion. Patients who are prescribed ZULRESSO are required to enroll in a registry which may allow us to compile additional information to further our understanding of the risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO and to improve management of the risk. Given the mode and setting of administration of ZULRESSO and the requirements of the REMS program, ZULRESSO has been administered to date primarily to treat women with severe PPD, and we expect that to continue to be the case. We estimate that about 20% to 30% of women diagnosed with PPD fall into this category.

In the second quarter of 2020, we received clearance from the FDA, under the Coronavirus Treatment Acceleration Program, or CTAP, to initiate a Phase 3 clinical trial with brexanolone in patients with advanced COVID-19 related acute respiratory distress syndrome, or ARDS. We expect to initiate patient dosing in this study in the fourth quarter of 2020. Topline data from this study are anticipated in 2021.

Our next most advanced product candidate is zuranolone (SAGE-217), an oral compound that is currently in Phase 3 clinical development for PPD and major depressive disorder, or MDD. Zuranolone is a novel neuroactive steroid that, like brexanolone, is a positive allosteric modulator of GABAA receptors that targets both synaptic and extrasynaptic GABAA receptors. The FDA has granted Breakthrough Therapy designation and Fast Track designation to zuranolone for the treatment of MDD. To date, we have completed three pivotal clinical trials of zuranolone, two in MDD and one in PPD. The first completed pivotal trial, a Phase 2 clinical trial evaluating zuranolone in the treatment of MDD, and a completed Phase 3 pivotal trial evaluating zuranolone in the treatment of PPD both met their primary endpoints. In each case, these trials evaluated the effect of zuranolone at a 30 mg dose. Our third pivotal trial of zuranolone, a Phase 3 clinical trial evaluating the effect of 30 mg of zuranolone on depressive symptoms in adults with MDD, known as the MOUNTAIN Study, did not meet its primary endpoint. Following discussions with the FDA, we determined to conduct three new Phase 3 clinical trials as part of our pivotal program for zuranolone in MDD and PPD:

- a placebo-controlled trial evaluating a two-week course of zuranolone 50 mg in women with PPD, with additional short-term follow-up, known as the SKYLARK Study;
- a placebo-controlled trial evaluating a two-week course of zuranolone 50 mg, when co-initiated with a newly administered standard antidepressant therapy, as an acute rapid response treatment in patients with MDD, with additional short-term follow-up, known as the CORAL Study; and
- a placebo-controlled trial evaluating a two-week course of zuranolone 50 mg in patients with MDD, with additional short-term follow-up, known as the WATERFALL Study.

We initiated patient dosing in the SKYLARK Study and the WATERFALL Study in the second quarter of 2020 and expect to initiate dosing in the CORAL Study in the fourth quarter of 2020. Topline results from these three studies are anticipated in 2021, with topline data from the WATERFALL Study expected in the first half of 2021.

We are also continuing our SHORELINE study, an open-label Phase 3 clinical trial evaluating the safety of as-needed repeat treatment with zuranolone in which patients with MDD receive an initial two-week course of zuranolone and responders from the first cycle are followed for up to one year and eligible to receive as-needed retreatment during the follow-up period. The need for repeated dosing is assessed every 14 days based on the results of a patient-reported PHQ-9 score (≥10) and 17-item Hamilton Rating Scale for Depression (HAMD-17) assessment (≥20). The protocol of the clinical trial requires a minimum of 56 days between zuranolone 14-day courses, to allow for a maximum of five treatments during the follow-up period. Enrollment of patients receiving the 30 mg dose in the SHORELINE study was completed in the third quarter of 2019. In May 2020, we amended the SHORELINE protocol to allow currently enrolled patients to receive retreatment with zuranolone 50 mg. Additionally, in the second quarter of 2020, we began enrolling a new cohort of patients with MDD in the SHORELINE Study who are to receive zuranolone 50 mg from the outset of their enrollment in the trial. In October 2020, we reported interim, topline results from a July 2020 data cut of the ongoing SHORELINE Study. For the primary endpoint of safety and tolerability, the analyzed data showed that zuranolone was generally well-tolerated in the 30 mg dose and among the initial patients treated with the 50 mg dose. Adverse events reported in the trial during the period analyzed were generally consistent with results seen in previous clinical trials of zuranolone, with the most common adverse events in the 30 mg group (observed in > 5% of subjects) including somnolence, headache and dizziness. The overall incidence of adverse events declined in subsequent treatment courses of zuranolone 30 mg. Events >5% of somnolence, dizziness, sedation, headache and tremor were observed to be more frequent in the 50 mg cohort, but were similar in severity to the events seen with patients receiving 30 mg doses. Most adverse events were mild or moderate. An increase in level of intensity of somnolence or sedation was also noted at the 50 mg dose in patients who had previously received a 30 mg dose. At the time of the data cut analysis, patients with a clinical response (decrease in HAMD-17 baseline score of ≥50%) at the end of the initial 14-day course of zuranolone 30 mg used a mean number of 1.9 treatments per year. We plan to report comprehensive data from the 30 mg dose in the first half of 2021 and will include additional subsets of data within the primary and secondary endpoints. Secondary endpoints included response and remission as evaluated by HAMD-17 and the number of times a patient received retreatment. We plan to report topline data from the 50mg dose in the second half of 2021.

In the fourth quarter of 2019, we paused enrollment in our REDWOOD study, a placebo-controlled Phase 3 clinical trial in MDD evaluating the efficacy (time to first relapse) and long-term safety of fixed interval zuranolone monotherapy maintenance treatment (treatment without traditional antidepressants) in which randomized patients receive a two-week course of zuranolone or placebo every two months until the first relapse for up to one year. We also paused enrollment in our RAINFOREST study, a placebo-controlled polysomnography Phase 3 clinical trial of zuranolone in patients with MDD who have co-morbid insomnia. We paused both of these studies, and have closed all clinical trial sites for these studies, to focus our resources and activities on enrollment in the three new Phase 3 clinical studies. We plan to evaluate whether to reinitiate the REDWOOD and RAINFOREST studies at a later date. We also continue to evaluate the ongoing zuranolone clinical pharmacology and safety program and plan to finalize requirements to support a potential future new drug application, or NDA, with the FDA.

In addition to zuranolone, 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, a disorder causing involuntary and rhythmic shaking, and, potentially, epileptiform disorders and Parkinson's disease. Based on the results of the Phase 1 clinical program, including a positive signal observed in a small cohort of patients with essential tremor and a safety profile consistent with GABAA positive allosteric modulation, and our other work in this area to date, in the second quarter of 2020, we began enrolling patients in a Phase 2 clinical trial evaluating SAGE-324 in the treatment of essential tremor, known as the KINETIC Study. Topline data from this study are expected in the first quarter of 2021. Our portfolio of novel GABAA receptor positive allosteric modulators also includes SAGE-689, a product candidate intended for intramuscular administration, and for which we have completed the non-clinical studies required to move into a Phase 1 clinical development program, and other compounds at earlier stages of development with a focus on both acute and chronic CNS disorders.

Our second area of focus for future clinical development 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 associated with NMDA receptor dysfunction, including Huntington's disease and Parkinson's disease. Examples of indications involving NMDA receptor dysfunction also include certain types, aspects or subpopulations of a number of diseases and disorders such as depression, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, and neuropathic pain. As part of our Phase 1 clinical program, we evaluated the safety, tolerability and pharmacokinetics of SAGE-718 in a small cohort of patients with early Huntington's disease. As part of this study, we also conducted assessments of executive functioning with measures relevant to the core cognitive decline observed in people with Huntington's disease. Based on the signals observed in this study and in similar measures during an earlier Phase 1 cohort of healthy volunteers without Huntington's disease, we initiated patient dosing in September 2020 in a Phase 2a open-label study of SAGE-718 evaluating patients with Parkinson's disease cognitive dysfunction, known as the PARADIGM Study, and plan to initiate dosing in a Phase 2a open-label clinical study of SAGE-718 in patients with Alzheimer's disease cognitive dysfunction and mild dementia, known as the LUMINARY Study, in the fourth quarter of 2020. We expect that data from the PARADIGM Study and the LUMINARY Study will inform potential advancement of SAGE-718 into further Phase 2 clinical development, including potentially in Huntington's disease. We expect to report topline data from the PARADIGM Study in the first quarter of 2021. Our second product candidate targeting the NMDA receptor, SAGE-904, is in development as a potential oral therapy for disorders associated with NMDA hypofunction. We initiated a Phase 1 clinical trial of SAGE-904 in healthy volunteers in the third quarter of 2019.

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 development opportunities in potential new areas of interest as well as to explore partnering opportunities where we believe a strategic partner may add significant value to our efforts, including through capabilities, infrastructure, speed or financial resources.

We began to generate revenue from product sales in the second quarter of 2019 in conjunction with the launch of our first product, ZULRESSO, 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 mid-2018 with Shionogi & Co., Ltd., or Shionogi, for the clinical development and commercialization of zuranolone in Japan, Taiwan and South Korea.

We have incurred net losses in each year since our inception, and we had an accumulated deficit of $2.0 billion as of September 30, 2020. Our net losses were $368.8 million for the nine months ended September 30, 2020 and $680.2 million for the year ended December 31, 2019. 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 we will incur significant expenses in the foreseeable future in connection with our ongoing activities, if and as we:

- continue to advance Phase 3 clinical development of zuranolone in PPD and MDD, and potentially advance zuranolone for other indications;
- continue our commercialization efforts with respect to ZULRESSO for the treatment of PPD in the U.S. with a primary focus in geographies that have existing, active ZULRESSO treating sites;
- advance SAGE-324 through completion of the ongoing KINETIC Study in essential tremor, with potential future development not only in essential tremor but also in certain epileptiform disorders, Parkinson’s disease and other neurological conditions;
- advance SAGE-718 through completion of the Phase 2a open-label PARADIGM Study of patients with Parkinson’s disease cognitive dysfunction, and through the planned initiation and completion of the Phase 2a open-label LUMINARY Study of patients with Alzheimer’s disease cognitive dysfunction and mild dementia, and potentially evaluate SAGE-718 in additional Phase 2 open-label clinical studies in patients with certain other cognition-related disorders, prior to determining potential next steps for advancing SAGE-718 further into Phase 2 clinical development, including potentially in Huntington’s disease;
- advance one or more non-clinical stage compounds into 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 product candidates, with the goal of developing a diversified portfolio of assets with differentiated features;
- continue to explore opportunities to establish agreements or alliances with pharmaceutical company collaborators or distributors for our product candidates where we believe the partnering opportunity will add significant value to our efforts, including through capabilities, infrastructure, speed or financial contributions;
- prepare for potential NDAs and pre-launch activities with respect to our product candidates at the appropriate time to support next steps if our pivotal programs are successful and support a filing;
- seek regulatory approvals for any product candidates that successfully complete clinical development;
- refine the formulation and improve the manufacturing process for our product candidates, and manufacture clinical supplies as development progresses;
- commercialize any product candidates for which we obtain regulatory approval, including the manufacture of commercial supplies;
- at the appropriate time if our development efforts progress successfully, 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.;
- continue to build, maintain, defend, leverage, and expand our intellectual property portfolio, including by utilizing the strengths of our proprietary chemistry platform and scientific know-how to expand our portfolio of new chemical entities to lessen our long-term reliance on the success of any one program and to facilitate long-term growth; and
- add or optimize operational, financial and management information systems.

Until such time that we can generate significant revenue from product sales, if ever, we expect to finance our operations primarily through a combination of revenue, equity or debt financings and other sources, which may include collaborations with third parties. We may not be successful in our commercialization of ZULRESSO or any other product, and may not generate meaningful revenue or revenue at the levels or on the timing necessary to support our investment and goals. We may never successfully complete development of any of our current or future product candidates, 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.

Financial Operations Overview

Revenue

We began to generate revenue from product sales in the second quarter of 2019 in conjunction with the launch of our first product, ZULRESSO, 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 mid-2018 with Shionogi.

Our revenue from sales of ZULRESSO has been negatively impacted by significant barriers arising from the complex requirements for treatment, and, more recently, by the spread of COVID-19 in the U.S. ZULRESSO is administered as a continuous infusion given over two and a half days. Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness during the ZULRESSO infusion, ZULRESSO must be administered only in a medically-supervised healthcare setting that has been certified under a REMS program and meets the other requirements of the REMS program, including requirements related to monitoring of the patient during the infusion. The actions required for a healthcare setting to be ready and willing to treat women with PPD are complex and time-consuming. These actions include: becoming REMS-certified; achieving formulary approvals; establishing protocols for administering ZULRESSO; and securing satisfactory reimbursement. Sites must often negotiate reimbursement on a payor-by-payor basis under commercial coverage. These requirements have created significant barriers to treatment, and are expected to continue to limit future revenue growth. These barriers have been compounded by the COVID-19 pandemic. The spread of COVID-19 in the U.S. has resulted in a significant number of sites of care pausing treatment of new patients with ZULRESSO. We believe concerns about exposure to the virus have also caused a significant reduction in the number of women with PPD seeking treatment with ZULRESSO and in physicians willing to prescribe it. Given the ongoing surges in the number of cases of COVID-19 in the U.S. and continuing concerns about the pandemic across the country, we expect the significant adverse impact of the pandemic on ZULRESSO revenues to continue. We anticipate that the COVID-19 pandemic will also continue to have an adverse impact on our results of operations from sales of ZULRESSO as pandemic-related restrictions are expected to continue to be in effect for the foreseeable future. The scope and timing of the expected negative impact will depend on, among other factors, the duration and severity of precautionary measures taken to curb the spread of COVID-19, the length and frequency of surges or waves of COVID-19 cases and the timing and success of any return to normal business operations across the U.S.

In April 2020, we implemented a workforce reduction that primarily affected the ZULRESSO commercial operation and related support functions, including eliminating the entire salesforce. While we remain committed to working with healthcare providers and women with PPD seeking access to ZULRESSO, our ongoing commercial efforts, including our small account management field-based team, are primarily focused on geographies that have existing, active ZULRESSO treating sites. We expect that this approach to our commercial efforts may continue to substantially limit the revenue opportunity for ZULRESSO.

We expect that ZULRESSO revenues are likely to fluctuate quarter to quarter. We will not generate revenue from other products unless and until we successfully develop, obtain regulatory approval of, and commercialize one of our current or future product candidates. If we enter into additional collaboration agreements with third parties for our product candidates, we may generate revenue from those collaborations. We expect that revenue, if any, that we may generate under 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.

Effective June 12, 2018, we entered into a strategic collaboration with Shionogi for the clinical development and commercialization of zuranolone for the treatment of MDD and other potential indications in Japan, Taiwan and South Korea. Under the terms of the agreement, Shionogi is responsible for all clinical development, regulatory filings and commercialization and manufacturing of zuranolone for MDD, and potentially other indications, in Japan, Taiwan and South Korea. On October 26, 2018, we also entered into a supply agreement with Shionogi for zuranolone clinical material. To date, revenue from the Company's collaboration with Shionogi has come from an initial, upfront license fee upon execution of the collaboration agreement of $90.0 million, which was recorded as collaboration revenue in the year ended December 31, 2018, and for the supply of API for Shionogi's clinical trials.

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 non-clinical studies and clinical trials and developing external manufacturing capabilities;
- costs of outside consultants engaged in research and development activities, including their fees and travel expenses;
- other expenses related to our non-clinical studies and clinical trials and expenses related to our regulatory activities;
- payments made under our third-party license agreements; and
- a portion of our facilities and other related expenses, including rent, depreciation, maintenance of facilities, insurance and supplies.

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 results of ongoing, planned or future clinical trials and non-clinical studies;
- decisions by regulatory authorities related to our product candidates;
- uncertainties in clinical trial enrollment rate or design;
- significant and changing government regulation; and
- the receipt and timing of regulatory approvals, if any.

In addition, the COVID-19 pandemic and the rapid spread of the virus in the U.S. and outside the U.S. may also negatively impact our ongoing and planned development activities and increase our research and development costs. Concerns, precautions and restrictions arising from the COVID-19 pandemic may substantially slow clinical site recruitment and initiation and enrollment in our clinical trials, may impair the conduct, auditing, monitoring, or completion of our trials, may impair or impede the timeliness and completion of our data collection and analysis efforts or the integrity of our data, or may cause us to pause trials, in each case which may significantly impact our ability to meet our expected timelines or cause us to change our plans and may significantly increase our research and development costs.

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

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

Selling, General and Administrative Expenses

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

In April 2020, we implemented a workforce reduction that primarily affected the ZULRESSO commercial operation and related support functions, including eliminating the entire salesforce. We expect the workforce reduction to reduce annualized operating expenses by approximately $170 million, of which $150 million is related to selling, general and administrative expenses. While we remain committed to working with healthcare providers and women with PPD seeking access to ZULRESSO, our ongoing commercial efforts, including our small account management field-based team, are primarily focused on geographies that have existing, active ZULRESSO treating sites. Even with the expected reduction in selling, general and administrative expenses as a result of the restructuring, we expect to continue to incur significant commercialization expenses, including payroll and related expenses, to support our ongoing commercial activities associated with ZULRESSO. We expect that selling, general and administrative expenses will increase in the future if we are successful in our development efforts and are preparing for potential commercialization of our current or future product candidates, if approved. We expect to continue to incur significant expenses associated with general operations, including costs related to accounting and legal services, director and officer insurance premiums, facilities and other corporate infrastructure and office-related costs, such as information technology costs.

Results of Operations

Comparison of the Three Months Ended September 30, 2020 and 2019

The following table summarizes our results of operations for the three months ended September 30, 2020 and 2019:

	Three Months Ended September 30, 2020	Three Months Ended September 30, 2019	Increase (Decrease)
	(in thousands)		
Product revenue, net	$ 1,639	$ 1,478	$ 161
Collaboration revenue	—	2,092	(2,092)
Total revenue	1,639	3,570	(1,931)
Operating costs and expenses:			
Cost of goods sold	149	137	12
Research and development	74,078	102,108	(28,030)
Selling, general and administrative	35,099	88,502	(53,403)
Restructuring	(529)	—	(529)
Total operating costs and expenses	108,797	190,747	(81,950)
Loss from operations	(107,158)	(187,177)	80,019
Interest income, net	1,347	7,227	(5,880)
Other income (expense), net	76	(8)	84
Net loss	$ (105,735)	$ (179,958)	$ 74,223

Product revenue, net

During the three months ended September 30, 2020 and 2019, we recognized $1.6 million and $1.5 million, respectively, of net product revenues related to sales of ZULRESSO. Sales allowances and accruals consisted of patient financial assistance, distribution fees, discounts and chargebacks.

Collaboration revenue

For the three months ended September 30, 2020, we recognized no collaboration revenue from our agreement with Shionogi. For the three months ended September 30, 2019, we recognized $2.1 million in collaboration revenue from our agreement with Shionogi related to the supply of zuranolone active pharmaceutical ingredient, or API, 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 in the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report.

Cost of goods sold

Cost of goods sold was $0.1 million for each of the three months ended September 30, 2020 and 2019, and is made up of a low-single digit royalty cost on net product revenue to CyDex and The Regents of the University of California, the amortization of intangible assets associated with ZULRESSO and third-party manufacturing and distribution costs associated with labeling, packaging, and shipping of ZULRESSO. Prior to receiving initial FDA approval for ZULRESSO on March 19, 2019, we manufactured ZULRESSO inventory to be sold upon commercialization and recorded approximately $8.9 million related to this inventory build-up as research and development expense. As a result, the manufacturing costs related to the ZULRESSO inventory build-up incurred before FDA approval were already expensed in a prior period and are therefore excluded from the cost of goods sold for the three months ended September 30, 2020 and 2019. We estimate our cost of goods sold as a percentage of net product revenue will remain in the mid-single digit percentage range for the foreseeable future. We expect to utilize zero cost inventory with respect to ZULRESSO for an extended period of time.

Research and development expenses

	Three Months Ended September 30, 2020	Three Months Ended September 30, 2019	Increase (Decrease)
	(in thousands)		
zuranolone (SAGE-217)	$ 31,343	$ 43,133	$ (11,790)
SAGE-324	5,509	8,212	(2,703)
SAGE-718	2,126	2,495	(369)
Other research and development programs	8,888	13,778	(4,890)
Unallocated expenses	16,285	17,379	(1,094)
Stock-based compensation	9,927	17,111	(7,184)
Total research and development expenses	$ 74,078	$ 102,108	$ (28,030)

Research and development expenses for the three months ended September 30, 2020 were $74.1 million, compared to $102.1 million for the three months ended September 30, 2019. The decrease of $28.0 million was primarily due to the following:

- a decrease of $11.8 million in expenses for zuranolone, primarily as a result of completion of the MOUNTAIN Study and decreased spending for clinical pharmacology studies, partially offset by an increase in spending for the WATERFALL Study;
- a decrease of $2.7 million in expenses for SAGE-324, primarily due to the completion of Phase 1 studies;
- a decrease of $4.9 million in expenses for other research and development programs, related to a decrease in spending on non-clinical studies and for brexanolone (SAGE-547); and
- a decrease of $7.2 million in non-cash stock-based compensation expense. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the three months ended September 30, 2020. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $4.5 million for the three months ended September 30, 2019. The remainder of the decrease is primarily from the impact of the cancellation of option grants that had been made to terminated employees, including those terminated in the restructuring.

Selling, general and administrative expenses

	Three Months Ended September 30, 2020	2019	Increase (Decrease)
	(in thousands)		
Personnel-related	$ 8,487	$ 31,780	$ (23,293)
Stock-based compensation	10,181	26,558	(16,377)
Professional fees	8,612	16,880	(8,268)
Other	7,819	13,284	(5,465)
Total selling, general and administrative expenses	$ 35,099	$ 88,502	$ (53,403)

Selling, general and administrative expenses for the three months ended September 30, 2020 were $35.1 million, compared to $88.5 million for the three months ended September 30, 2019. The decrease of $53.4 million was primarily due to the following:

- a decrease of $23.3 million in personnel-related costs, mainly as a result of the termination of employees in the restructuring;
- a decrease of $16.4 million in non-cash stock-based compensation expense. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the three months ended September 30, 2020. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $6.4 million during the three months ended September 30, 2019. The remainder of the decrease is primarily from the impact of the cancellation of option grants that had been made to terminated employees, including those terminated in the restructuring;
- a decrease of $8.3 million in professional fees, primarily due to the impact of the restructuring on our spending for commercial activities; and
- a decrease of $5.5 million in other costs, primarily due to the impact of the restructuring and the impact of the COVID-19 pandemic resulting in our employees working remotely and a reduction in business travel.

Interest income, net and Other income (expense), net

Interest income, net, and other expense, net, for the three months ended September 30, 2020 and 2019 were $1.4 million and $7.2 million, respectively. The primary reason for the decrease was the decrease in the balance of marketable securities and a reduction in interest rates.

Comparison of the Nine Months Ended September 30, 2020 and 2019

The following table summarizes our results of operations for the nine months ended September 30, 2020 and 2019:

	Nine Months Ended September 30, 2020	Nine Months Ended September 30, 2019	Increase (Decrease)
	(in thousands)		
Product revenue, net	$ 5,014	$ 1,997	$ 3,017
Collaboration revenue	—	2,911	(2,911)
Total revenue	5,014	4,908	106
Operating costs and expenses:			
Cost of goods sold	429	181	248
Research and development	211,008	277,565	(66,557)
Selling, general and administrative	143,454	260,648	(117,194)
Restructuring	27,873	—	27,873
Total operating costs and expenses	382,764	538,394	(155,630)
Loss from operations	(377,750)	(533,486)	155,736
Interest income, net	8,763	21,889	(13,126)
Other income, net	165	12	153
Net loss	$ (368,822)	$ (511,585)	$ 142,763

Product revenue, net

During the nine months ended September 30, 2020 and 2019, we recognized $5.0 million and $2.0 million, respectively, of net product revenues related to sales of ZULRESSO. Sales allowances and accruals consisted of patient financial assistance, distribution fees, discounts and chargebacks.

Collaboration revenue

For the nine months ended September 30, 2020, we recognized no collaboration revenue from our agreement with Shionogi. For the nine months ended September 30, 2019, we recognized $2.9 million in collaboration revenue from our agreement with Shionogi related to the supply of zuranolone API 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 in the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report.

Cost of goods sold

Cost of goods sold was $0.4 million and $0.2 million for the nine months ended September 30, 2020 and 2019, respectively, and is made up of a low-single digit royalty cost on net product revenue to CyDex and The Regents of the University of California, the amortization of intangible assets associated with ZULRESSO and third-party manufacturing and distribution costs associated with labeling, packaging, and shipping of ZULRESSO. Prior to receiving initial FDA approval for ZULRESSO on March 19, 2019, we manufactured ZULRESSO inventory to be sold upon commercialization and recorded approximately $8.9 million related to this inventory build-up as research and development expense. As a result, the manufacturing costs related to the ZULRESSO inventory build-up incurred before FDA approval were already expensed in a prior period and are therefore excluded from the cost of goods sold for the nine months ended September 30, 2020 and 2019. We estimate our cost of goods sold as a percentage of net product revenue will remain in the mid-single digit percentage range for the foreseeable future. We expect to utilize zero cost inventory with respect to ZULRESSO for an extended period of time.

Research and development expenses

	Nine Months Ended September 30, 2020	Nine Months Ended September 30, 2019	Increase (Decrease)
		(in thousands)	
zuranolone (SAGE-217)	$ 83,402	$ 110,813	$ (27,411)
SAGE-324	12,664	15,490	(2,826)
SAGE-718	4,296	9,444	(5,148)
Other research and development programs	25,432	35,515	(10,083)
Unallocated expenses	52,944	54,775	(1,831)
Stock-based compensation	32,270	51,528	(19,258)
Total research and development expenses	$ 211,008	$ 277,565	$ (66,557)

Research and development expenses for the nine months ended September 30, 2020 were $211.0 million, compared to $277.6 million for the nine months ended September 30, 2019. The decrease of $66.6 million was primarily due to the following:

- a decrease of $27.4 million in expenses for zuranolone, primarily as a result of completion of the MOUNTAIN Study and decreased spending for clinical pharmacology studies, partially offset by an increase in spending for the WATERFALL Study;
- a decrease of $2.8 million in expenses for SAGE-324, primarily due to the completion of Phase 1 studies;
- a decrease of $5.1 million in expenses for SAGE-718, primarily due to the completion of Phase 1 studies during 2019;
- a decrease of $10.1 million in expenses for other research and development programs, related to a decrease in spending on non-clinical studies and for brexanolone (SAGE-547); and
- a decrease of $19.3 million in non-cash stock-based compensation expense. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the nine months ended September 30, 2020. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $14.0 million for the nine months ended September 30, 2019. The remainder of the decrease is primarily from the impact of the cancellation of option grants that had been made to terminated employees, including those terminated in the restructuring.

Selling, general and administrative expenses

	Nine Months Ended September 30, 2020	Nine Months Ended September 30, 2019	Increase (Decrease)
		(in thousands)	
Personnel-related	$ 49,492	$ 93,945	$ (44,453)
Stock-based compensation	41,192	71,024	(29,832)
Professional fees	26,371	55,926	(29,555)
Other	26,399	39,753	(13,354)
Total selling, general and administrative expenses	$ 143,454	$ 260,648	$ (117,194)

Selling, general and administrative expenses for the nine months ended September 30, 2020 were $143.5 million, compared to $260.6 million for the nine months ended September 30, 2019. The decrease of $117.2 million was primarily due to the following:

- a decrease of $44.5 million in personnel-related costs, mainly as a result of the termination of employees in the restructuring;
- a decrease of $29.8 million in non-cash stock-based compensation expense. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the nine months ended September 30, 2020. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $13.2 million during the nine months ended September 30, 2019. The remainder of the decrease is primarily from the impact of the cancellation of option grants that had been made to terminated employees, including those terminated in the restructuring;
- a decrease of $29.6 million in professional fees, primarily due to costs incurred in the nine months ended September 30, 2019, related to preparations for the commercial launch of ZULRESSO in the U.S., which commenced on June 24, 2019 and the impact of the restructuring on our spending for commercial activities; and
- a decrease of $13.4 million in other costs, primarily due to the impact of the restructuring and the impact of the COVID-19 pandemic resulting in our employees working remotely and a reduction in business travel.

Restructuring

In April 2020, we announced a restructuring plan to enable us to advance our corporate strategy and pipeline that included the elimination of approximately 53% of our workforce. The workforce reduction primarily affected the ZULRESSO commercial operation and related selling, general and administrative support functions. In the nine months ended September 30, 2020, we recorded $27.9 million of expense, primarily for one-time termination benefits to the affected employees, primarily for cash payments of severance, healthcare benefits and outplacement assistance.

Interest income, net and Other income (expense), net

Interest income, net, and other expense, net, for the nine months ended September 30, 2020 and 2019 were $8.9 million and $21.9 million, respectively. The primary reason for the decrease was the decrease in the balance of marketable securities and a reduction in interest rates.

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 the 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 September 30, 2020, we had an accumulated deficit of $2.0 billion. From our inception through September 30, 2020, we received net proceeds of $2.2 billion from the sales of redeemable convertible preferred stock prior to our initial public offering, the issuance of convertible notes and the sales of common stock in our initial public offering in July 2014 and follow-on offerings.

On February 27, 2019, we completed the sale of 3,833,334 shares of our common stock in a follow-on 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 September 30, 2020, our primary sources of liquidity were our cash, cash equivalents and marketable securities, which totaled $668.5 million. We invest our cash in money market funds, U.S. government securities, corporate bonds and commercial paper, with the primary objectives to preserve principal, provide liquidity and maximize income without significantly increasing risk.

The following table summarizes the primary sources and uses of cash for the nine months ended September 30, 2020 and 2019:

	Nine Months Ended September 30, 2020	2019
	(in thousands)	
Net cash provided by (used in):		
Operating activities	$ (346,691)	$ (411,980)
Investing activities	397,165	(125,240)
Financing activities	7,091	605,458
Total	$ 57,565	$ 68,238

Operating Activities

During the nine months ended September 30, 2020, net cash used in operating activities primarily resulted from our net loss of $368.8 million, which was primarily attributable to our research and development activities and our selling, general and administrative expenses, and changes in our operating assets and liabilities of $54.7 million, partially offset by $76.8 million of non-cash items. During the nine months ended September 30, 2019, net cash used in operating activities primarily resulted from our net loss of $511.6 million, which was primarily attributable to our research and development activities and our selling, general and administrative expenses, and changes in our operating assets and liabilities of $15.5 million, partially offset by $115.1 million of non-cash items.

Investing Activities

During the nine months ended September 30, 2020 and 2019, net cash provided by investing activities was $397.2 million and net cash used in investing activities was $125.2 million, respectively. During the nine months ended September 30, 2020 and 2019, 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 follow-on underwritten public offering in February 2019.

Financing Activities

During the nine months ended September 30, 2020 and 2019, net cash provided by financing activities was $7.1 million and $605.5 million, respectively. During the nine months ended September 30, 2019, we received $560.9 million of net proceeds from our follow-on underwritten public offering, after deducting commissions and underwriting discounts and offering costs paid by us.

Operating Capital Requirements

We began to generate revenue from product sales in the second quarter of 2019 in conjunction with the launch of our first product, ZULRESSO. 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 significant costs associated with general operations. In addition, we expect to incur significant commercialization expenses for product sales, marketing and outsourced manufacturing with respect to ZULRESSO 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 September 30, 2020, will enable us to fund our operating expenses and capital expenditure requirements into 2022. During that time, we expect to incur significant expenses as we:

- continue to advance Phase 3 clinical development of zuranolone in PPD and MDD, and potentially advance zuranolone for other indications;
- continue our commercialization efforts with respect to ZULRESSO for the treatment of PPD in the U.S. with a primary focus in geographies that have existing, active ZULRESSO treating sites;
- advance SAGE-324 through completion of the ongoing KINETIC Study in essential tremor, with potential future development not only in essential tremor but also in certain epileptiform disorders, Parkinson’s disease and other neurological conditions;
- advance SAGE-718 through completion of the Phase 2a open-label PARADIGM Study of patients with Parkinson’s disease cognitive dysfunction, and through the planned initiation and completion of the Phase 2a open-label LUMINARY Study of patients with Alzheimer’s disease cognitive dysfunction and mild dementia, and potentially evaluate SAGE-718 in additional Phase 2 open-label clinical studies in patients with certain other cognition-related disorders, prior to determining potential next steps for advancing SAGE-718 further into Phase 2 clinical development, including potentially in Huntington’s disease;
- advance one or more non-clinical stage compounds into 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 product candidates, with the goal of developing a diversified portfolio of assets with differentiated features;
- continue to explore opportunities to establish agreements or alliances with pharmaceutical company collaborators or distributors for our product candidates where we believe the partnering opportunity will add significant value to our efforts, including through capabilities, infrastructure, speed or financial contributions;
- prepare for potential NDAs and pre-launch activities with respect to our product candidates at the appropriate time to support next steps if our pivotal programs are successful and support a filing;
- seek regulatory approvals for any product candidates that successfully complete clinical development;
- refine the formulation and improve the manufacturing process for our product candidates, and manufacture clinical supplies as development progresses;
- commercialize any product candidates for which we obtain regulatory approval, including the manufacture of commercial supplies;
- at the appropriate time if our development efforts progress successfully, 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.;
- continue to build, maintain, defend, leverage and expand our intellectual property portfolio, including by utilizing the strengths of our proprietary chemistry platform and scientific know-how to expand our portfolio of new chemical entities to lessen our long-term reliance on the success of any one program and to facilitate long-term growth; and
- add or optimize operational, financial and management information systems.

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, which will be impacted by a number of factors, including: the rate, degree and level of market acceptance for ZULRESSO for the treatment of PPD in the U.S.; the impact of our April 2020 restructuring and the decision to focus our efforts primarily on geographies in the U.S. that have existing, active ZULRESSO treating sites; the continued availability of healthcare settings in those geographies to administer ZULRESSO and the ability and willingness of such healthcare settings to make sufficient capacity available; the level of reimbursement for both ZULRESSO and the infusion in the healthcare setting both by commercial and government payors, and the nature of limitations on reimbursement; the number of healthcare professionals willing to prescribe ZULRESSO and women with PPD who agree to be treated with ZULRESSO; and the scope, duration and timing of the impact of the COVID-19 pandemic;
- the timing and amount of costs associated with our commercialization of ZULRESSO;
- the initiation, progress, timing, costs, and results of ongoing, planned and future non-clinical studies and clinical trials for zuranolone and our other existing and future product candidates; the number and length of clinical trials required by regulatory authorities to support regulatory approval; and the costs of preparing regulatory filings;
- the length, severity and costs of disruptions, if any, associated with the COVID-19 pandemic on initiation and conduct of our clinical trials;
- the ability of zuranolone 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 permitted prelaunch activities and preparing for a potential future commercial launch of any such product candidate that is successfully developed and approved;
- the size of the PPD market and the portion of the population for which ZULRESSO may be prescribed; the size of the markets for which zuranolone and our other product candidates may be approved in the future, if successfully developed; the portion of the population in the approved indications for which our future 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 also finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other sources of funding. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or in light of other strategic considerations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and may require the issuance of warrants, which could potentially dilute the ownership interest of our stockholders. If we raise additional funds through collaborations, strategic alliances 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. Raising funds in the current economic environment may present challenges. The COVID-19 pandemic has caused major volatility in the stock market and a significant global economic downturn. If the economic downturn caused by the pandemic continues for an extended period or surges in the number of cases of COVID-19 continue or worsen in the future, or if our business prospects are impaired or the capital markets disrupted for other reasons, additional capital may not be available to us on acceptable terms, or at all. 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.

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 condensed consolidated financial statements in accordance with accounting principles generally accepted in the U.S. Our preparation of these condensed 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 condensed 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.

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 – Critical Accounting Policies and Significant Judgments and Estimates” included in our Annual Report.

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 Part I, Item 1 of this Quarterly Report.

Item 3. Quantitative and Qualitative Disclosures about Market Risk

We had cash, cash equivalents and marketable securities of approximately $668.5 million as of September 30, 2020. The primary objectives of our investment activities are to preserve principal, provide liquidity and maximize income without significantly increasing risk. Our primary exposure to market risk relates to fluctuations in interest rates, which are affected by changes in the general level of U.S. interest rates. Given the short-term nature of our cash, cash equivalents and marketable securities, we do not expect that a sudden change in market interest rates would have a material impact on our financial condition and/or results of operations. We do not own any derivative financial instruments.

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

We do not believe that our cash, cash equivalents and marketable securities have significant risk of default or illiquidity. While we believe our cash, cash equivalents and marketable securities do not contain excessive risk, we cannot provide absolute assurance that in the future our investments will not be subject to adverse changes in market value. In addition, we maintain significant amounts of cash, cash equivalents and marketable securities 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 nine months ended September 30, 2020 and 2019.

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

As of September 30, 2020, our management, with the participation of our principal executive officer and principal financial and accounting officer, evaluated the effectiveness of our disclosure controls and procedures. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our principal executive officer and principal financial and accounting officer have concluded, based upon the evaluation described above, that, as of September 30, 2020, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control over Financial Reporting

There were no changes to our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Securities Exchange Act of 1934) that occurred during the period covered by this Quarterly Report that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting. As a result of the COVID-19 pandemic, in March 2020, most of our employees began working remotely. We have not identified any material changes in our internal control over financial reporting as a result of these changes to the working environment. We are continually monitoring and assessing the COVID-19 situation to determine any potential impacts on the design and operating effectiveness of 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 September 30, 2020, 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

There is no assurance that our commercialization efforts in the U.S. with respect to ZULRESSO® (brexanolone) CIV injection will be successful or that we will ever be able to generate meaningful revenues or revenues at levels or on timing necessary to support our investment and goals.

Our first product, ZULRESSO, was approved by the Food and Drug Administration, or FDA, in March 2019 as a treatment for postpartum depression, or PPD, and was made commercially available beginning on June 24, 2019. There is no assurance that we will ever be able to generate meaningful revenues or revenues at levels or on timing necessary to support our investment and goals. Our revenue from sales of ZULRESSO has been negatively impacted by significant barriers arising from the complex requirements for treatment and, more recently, by the rapid spread of COVID-19 in the U.S., and these factors are expected to continue to impact revenues negatively in the future. ZULRESSO is administered as a continuous infusion given over two and a half days. Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness during the ZULRESSO infusion, ZULRESSO is approved for administration only in a medically-supervised healthcare setting that has been certified under a Risk Evaluation and Mitigation Strategy, or REMS, program and meets the other requirements of the REMS program, including requirements related to monitoring of the patient during the infusion. The actions required for a healthcare setting to be ready and willing to treat women with PPD are complex and time-consuming. These actions include becoming REMS-certified; achieving formulary approvals; establishing protocols for administering ZULRESSO; and securing satisfactory reimbursement. Sites must often negotiate reimbursement on a payor-by-payor basis under commercial coverage. These requirements have created significant barriers to treatment. We expect these barriers will continue to negatively impact ZULRESSO revenue growth, but we do not know the extent of the anticipated impact. These barriers have been compounded by the COVID-19 pandemic. The spread of COVID-19 in the U.S. has resulted in a significant number of sites of care pausing treatment of new patients with ZULRESSO. We believe concerns about exposure to the virus have also caused a significant reduction in the number of women with PPD seeking treatment with ZULRESSO and in physicians willing to prescribe it. Given the ongoing surges in the number of cases of COVID-19 in the U.S. and continuing concerns about the pandemic across the country, we expect the significant adverse impact of the pandemic on ZULRESSO revenues to continue. Specifically, we anticipate that the COVID-19 pandemic will continue to have an adverse impact on our results of operations from sales of ZULRESSO as pandemic-related restrictions are expected to continue to be in effect for the foreseeable future. The scope and timing of the expected negative impact will depend on, among other factors, the duration and severity of precautionary measures taken to curb the spread of COVID-19, the length and frequency of surges or waves of COVID-19 cases and the timing and success of any return to normal business operations across the

U.S. Given the rapid development and continued fluidity of the COVID-19 pandemic, we cannot predict its course or for how long and to what extent it will have an adverse impact on ZULRESSO sales.

In April 2020, we implemented a workforce reduction that primarily affected the ZULRESSO commercial operation and related support functions, including eliminating the entire salesforce. While we remain committed to working with healthcare providers and women with PPD seeking access to ZULRESSO, our ongoing commercial efforts, including our small account management field-based team, are primarily focused on geographies that have existing, active ZULRESSO treating sites. We expect that this approach to our commercial efforts may continue to substantially limit the revenue opportunity for ZULRESSO. Our post-restructuring focus primarily on geographies where there are existing, active ZULRESSO treating sites may make it difficult for us to achieve revenue growth from ZULRESSO. Given the shift in focus of our commercial efforts, the number of new healthcare settings that become treating sites for ZULRESSO, if any, may be limited. We may also find that certain healthcare settings that have in the past been active treating sites may not be willing to remain infusion-ready as a result of the complex requirements related to administration of ZULRESSO and compliance with the REMS, related limitations and restrictions, or because of actual or perceived difficulties obtaining satisfactory reimbursement or limitations on reimbursement or for other reasons. Healthcare settings that are active sites may also limit capacity used for ZULRESSO infusions or wait to gain familiarity with the clinical profile of ZULRESSO and to secure direct experience with reimbursement prior to increasing patient intake.

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. 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. In addition, more healthcare providers than we expected have been unwilling to accept a new treatment paradigm for women with PPD and this may continue. We believe this unwillingness is due primarily to the product profile and reimbursement challenges associated with ZULRESSO. Further, 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 be focused primarily on women with more severe symptoms of PPD. We may also encounter challenges from both commercial and government payors related to reimbursement of ZULRESSO, even from payors who have provided prior positive signals, including restrictions related to the severity of PPD cases for which ZULRESSO will be reimbursed or requiring use of other treatments prior to ZULRESSO or applying other limitations in the scope, breadth, availability or amount of reimbursement covering ZULRESSO or the infusion. For example, the availability, terms and timing of coverage for ZULRESSO by state Medicaid systems is expected to continue to vary significantly by state, and we may encounter states that impose significant restrictions or lengthy delays. Similarly, healthcare settings or patients may determine that the financial burdens of treatment are not acceptable. For example, a number of healthcare settings that are willing to administer ZULRESSO to women with PPD who have commercial insurance do not currently treat Medicaid patients, which may affect our ability to generate revenue from ZULRESSO.

We may face other limitations or issues related to sales 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. We may be unable to comply with our obligations under the ZULRESSO REMS, which include auditing of healthcare settings, collection and analysis of required data, and other requirements, to the satisfaction of the FDA, or the FDA may require modifications to or additional restrictions under the ZULRESSO REMS, any of which could materially adversely affect our business and results of operations.

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

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 zuranolone (SAGE-217) is in Phase 3 clinical development for major depressive disorder, or MDD, and PPD, and may be explored in other indications; and other product candidates are at earlier stages. We cannot be certain that we will be able to initiate planned clinical trials, to complete ongoing clinical trials or to announce results of such trials, with respect to zuranolone or any of our other product candidates, on the timelines we expect or at all or that the results of our development programs will be positive or that the design or results of our 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 current or future 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 zuranolone 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 zuranolone 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 clinical trials or interim results of clinical trials may not be repeated or observed in ongoing, future or completed studies or trials involving the same compound or other product candidates. Some or all of our clinical trials may fail to meet their primary or key secondary endpoints, raise safety issues or generate mixed results. For example, in December 2019, we announced that the MOUNTAIN Study, a Phase 3 clinical trial of zuranolone for the treatment of MDD, did not meet its primary endpoint. The results of clinical trials or non-clinical studies of our product candidates at any stage may not support further development or may not be sufficient to file for and obtain regulatory approval. Even if we conduct the trials required by or discussed with the FDA, the FDA may ultimately decide that the design, number and type of trials, number of patients studied or results, even if positive, are not sufficient to file for or gain regulatory approval of zuranolone in MDD and PPD or of any of our other product candidates in the indications we may study, or do not support the safety or efficacy or our intended profile for the product. We also may not be able to meet the requirements for non-clinical data or clinical data needed to advance such a development program. We may find that studying alternate formulations of our product candidates or doses that achieve higher or lower patient exposure—for example evaluating a 50 mg dose in our pivotal Phase 3 clinical trials for zuranolone, which is expected to achieve higher patient exposures than previously observed in patients enrolled in our prior multi-dose trials of zuranolone, as we have been doing in our ongoing Phase 3 WATERFALL Study and Phase 3 open-label SHORELINE Study, or evaluating new doses in our Phase 2 study of SAGE-324 in essential tremor, or as we might decide to do with other programs in the future—may result in unexpected adverse events or raise other safety issues or may otherwise generate negative results. In the case of zuranolone, we may encounter issues with the efficacy or durability of short-term treatment, or co-initiated treatment with zuranolone and traditional antidepressants, or safety and efficacy concerns with respect to retreatment that require additional studies be conducted or cause us not to continue our efforts.

Changes in formulation or the need to refine or scale-up the manufacturing process as we do for any of our product candidates could also delay development or require us to conduct additional clinical trials or non-clinical studies or conduct post-approval analyses, or could lead to different results than achieved with the earlier formulation or processes. We may not be able to initiate or complete our clinical trials or announce results from our clinical trials on the timelines we expect. We may experience slower than expected recruitment of sites or enrollment and randomization of patients in our clinical trials, particularly in clinical trials where an in-patient stay or frequent site visits are required, the patient population is small, enrollment criteria are more selective than historically used or there are existing therapies. These types of delays can lead to delays in initiation and 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 COVID-19 pandemic and the rapid spread of the virus in the U.S. and outside the U.S. may negatively impact our ongoing and planned development activities. Some clinical sites may decline or delay participation in our trials so as to prioritize medical resources to the treatment of COVID-19 patients or as a result of recommended or required restrictions on nonessential businesses. Concerns about COVID-19 and related precautions and restrictions may also make it difficult to enroll patients in our clinical trials or may increase the rates of patients withdrawing from our clinical trials following enrollment. These concerns, precautions and restrictions arising from the COVID-19 pandemic may substantially slow clinical site recruitment and initiation and enrollment in our clinical trials, or cause us to pause trials, in each case which may significantly impact our ability to meet our expected timelines or may significantly impact our costs or other aspects of our business or cause us to have to change our plans. In response to the COVID-19 pandemic or as a result of restrictions imposed or recommended by federal, state or local authorities, we or our clinical sites may also decide to take steps to minimize the number of visits a clinical trial participant is required to make to a site, including by limiting or modifying clinical trial procedures and visits for data collection. Similarly, clinical sites may impose other restrictions or limitations on key clinical trial activities such as monitoring of the sites by clinical research organizations. Limitations or modifications to study procedures, study visits or data collection, restrictions on key clinical trial activities such as monitoring or auditing, or other restrictions that may affect data analysis activities may require additional assessment and evaluation from institutional review boards; negatively impact the integrity or completeness of our trial data, the powering of a trial, the integrity or relevance of clinical study endpoints; or impact the timing of availability of results.

The drug development process can take many years, and may include post-marketing studies and surveillance, which will require the expenditure of substantial resources. Of the large number of drugs in development in the U.S., only a small percentage will successfully complete the FDA regulatory approval process and will be commercialized. Accordingly, even if we have the requisite financial resources, when needed, to continue to fund our development efforts, we cannot assure you that any of our current or future product candidates will be successfully developed or commercialized either in the U.S. or in any country outside the U.S.

Even if we 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 a New Drug Application, or 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 of the FDA, 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 for our product candidates, or may modify an existing REMS;
- the FDA or applicable foreign regulatory authorities may determine that the manufacturing processes or facilities of third-party contract manufacturers with which we contract do not conform to applicable requirements, including 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 U.S. Drug Enforcement Administration, or DEA, will need to determine the controlled substance schedule of the product, taking into account the recommendation of the FDA. The timing of the scheduling process 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. We may never file a marketing authorization application, or MAA, seeking approval of brexanolone, zuranolone 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 we 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, rebates or other hurdles or restrictions on reimbursement. Failure to obtain marketing and pricing approval in countries outside the U.S. without onerous restrictions or limitations related to pricing, or any delay or other setback in obtaining such approval, would impair our ability 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.

The COVID-19 pandemic may continue to adversely impact our business, including our sales of ZULRESSO and our initiation, conduct and completion of non-clinical studies and clinical trials.

The spread of COVID-19 in the U.S. has resulted in a significant number of sites of care pausing treatment of new patients with ZULRESSO. We believe concerns about exposure to the virus have also caused a significant reduction in the number of women with PPD seeking treatment with ZULRESSO and in physicians willing to prescribe it. Given the ongoing surges in the number of cases of COVID-19 in the U.S. and continuing concerns about the pandemic across the country, we expect the significant adverse impact of the pandemic on ZULRESSO revenues to continue. We anticipate that the COVID-19 pandemic will also continue to have an adverse impact on our results of operations from sales of ZULRESSO as pandemic-related restrictions are expected to continue to be in effect for the foreseeable future. The scope and timing of the expected negative impact will depend on, among other factors, the duration and severity of precautionary measures taken to curb the spread of COVID-19, the length and frequency of surges or waves of COVID-19 cases and the timing and success of any return to normal business operations across the U.S. Given the rapid development and continued fluidity of the COVID-19 pandemic, we cannot predict its course or for how long and to what extent it will have an adverse impact on ZULRESSO sales.

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

- delays or difficulties in recruiting clinical sites and in clinical site initiation due to prioritization of medical resources to the treatment of COVID-19 patients or as a result of recommended or required precautions or limitations intended to curb the spread of the virus;
- delays or difficulties in enrolling patients in our clinical trials, or an increase in the number of patients who withdraw from our clinical trials prior to completion as a result of concerns about COVID-19 or as a result of recommended or required precautions or limitations intended to curb the spread of the virus, or the potential that patients in our trials may have or contract COVID-19 which may impact the trial results;
- delays or disruptions in non-clinical studies due to precautions taken by contract research organizations or other vendors in light of the spread of COVID-19 or related restrictions recommended or imposed by federal, state or local authorities;

- limitations or modifications to study procedures, the number and type of study visits or data collection or data analysis activities, or other restrictions on other key clinical trial activities such as monitoring and auditing, in response to the COVID-19 pandemic or as a result of restrictions imposed or recommended by federal, state or local governments;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites, laboratories or other vendors providing testing services and hospital staff who would otherwise be available to support the conduct of our clinical trials;
- interruption or delays in the operations of the FDA and comparable foreign regulatory agencies, which may impact timelines for initiation of clinical trials or amendments of protocols;
- interruption of, or delays in, availability of supplies of our product candidates if the COVID-19 pandemic continues in surges or recurs in waves for an extended period, including the potential for shortages of raw materials, other drugs or materials used in our clinical trials, including the standard antidepressant therapy being assessed in combination with zuranolone in the CORAL Study, or staff available to our contract manufacturing organizations or other vendors in the supply chain or as the result of restrictions or limitations in their businesses or activities; and
- limitations on employee resources that would otherwise be focused on the conduct of our non-clinical studies and clinical trials, including because of sickness of employees or their families, or employees taking leaves as a result of the COVID-19 pandemic, and an increased reliance on working from home.

The COVID-19 pandemic has caused major volatility in the stock market and a significant global economic downturn. If the economic downturn caused by the pandemic continues for an extended period or surges in the number of cases of COVID-19 continue or worsen in the future, or if our business prospects are impaired or the capital markets disrupted for other reasons, additional capital may not be available to us on acceptable terms, or at all. We expect to need to raise additional funding at some point in the future. 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.

These and other factors arising from the COVID-19 pandemic could worsen or could arise in multiple waves even after the virus is partially contained.

A Breakthrough Therapy designation or Fast Track designation by the FDA or PRIority MEdicines, or PRIME, designation by the European Medicines Agency, or 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 zuranolone for the treatment of MDD. We have received PRIME designation from the EMA in the EU for our proprietary formulation of brexanolone as a potential treatment for PPD. In the future, we may seek Fast Track, Breakthrough Therapy or PRIME designations for zuranolone 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 MDD, essential tremor and the other diseases and disorders for which we are developing our product candidates have 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 or on the timing we expect could be materially adversely impacted. If the actual number of patients with MDD, essential tremor or the other diseases or disorders we are pursuing or 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, zuranolone, for the treatment of MDD, PPD, and other potential indications. We are developing SAGE-324 as a potential oral therapy for neurological conditions, such as essential tremor, epilepsy and Parkinson's disease. We are exploring SAGE-718 as a potential treatment for certain cognition-related disorders associated with NMDA receptor dysfunction, including Huntington's disease and Parkinson's disease. There is no precise method of establishing the actual number of patients with any of these disorders in any geography over any time period. With respect to PPD, MDD, essential tremor and many of the other indications in which we are developing, or plan to develop, our product candidates, we have or will provide estimates of the prevalence of the disease or disorder. Our estimates as to prevalence may not be accurate, and the actual prevalence or addressable patient population for some or all of those indications, or any other indication that we elect to pursue, may be significantly smaller than our estimates. In estimating the potential prevalence of indications we are pursuing, or may in the future pursue, including our estimates as to the prevalence of PPD, MDD and essential tremor, 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, essential tremor 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; reimbursement restrictions; and the cost of therapy compared to lower cost antidepressants may continue to limit the type of women who are prescribed ZULRESSO or who actually receive treatment to those patients with more severe symptoms of PPD. 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 the level and timing of 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, non-clinical studies, expanded access programs or investigator-sponsored 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, could make it more difficult for us to enroll patients in our clinical trials, or could require us to conduct additional non-clinical studies or clinical trials as part of our development program. 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 in the same indications or other indications. Interim results from nonclinical studies and clinical trials may not be predictive of results of such non-clinical studies or clinical trials once completed. If we cannot replicate the positive results from our earlier non-clinical studies and clinical trials of our product candidates in our later non-clinical studies and clinical trials in the same indications or other indications, or we cannot replicate our interim results in our completed non-clinical studies and clinical trials, we may be unable to successfully develop, obtain regulatory approval for and commercialize our product candidates.

Positive results from non-clinical studies and clinical trials of our product candidates may not necessarily be predictive of the results we may obtain from subsequent non-clinical studies or clinical trials using the same product candidate or other product candidates. By way of example, unlike earlier trials of zuranolone in MDD and PPD, the Phase 3 MOUNTAIN Study evaluating zuranolone in patients with MDD did not meet its primary endpoint. We may find that ongoing or future clinical trials of zuranolone or any of our other product candidates may also fail to meet their primary endpoints. Similarly, we received clearance from the FDA, under the Coronavirus Treatment Acceleration Program, or CTAP, to initiate a Phase 3 clinical trial with brexanolone in patients with advanced COVID-19 related acute respiratory distress syndrome, or ARDS. We are planning to study brexanolone in the treatment of advanced COVID-19-related ARDS based on our analysis of earlier preclinical data and clinical data from a different indication, and there is no guarantee that brexanolone will be able to mitigate the morbidity and mortality associated with advanced COVID-19-related ARDS. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later-stage clinical trials after achieving positive results in earlier-stage development, and we cannot be certain that we will not face similar setbacks. Similarly, interim results from nonclinical studies and clinical trials may not be predictive of results of a non-clinical study or clinical trial once completed. These setbacks in drug development 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. 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, or a different rate or severity of events, including as a result of an increase in dosing, studying a different patient population or different indication than previously studied, or administering a product candidate with a concomitant medication. For example, as part of ongoing development efforts, we are currently evaluating a 50 mg dose in our pivotal Phase 3 clinical trials for zuranolone, which is expected to achieve higher patient exposures than previously observed in patients enrolled in our prior multi-dose trials of zuranolone. We are also evaluating new dose of SAGE-324 in our Phase 2 study in essential tremor. In addition, we are planning to study brexanolone in patients with advanced COVID-19 related ARDS, which we have not previously studied. These studies may result in unexpected adverse events or raise other safety issues or may otherwise generate negative results. The results from non-clinical animal models may not be replicated in clinical trials. Many product candidates, including many targeting central nervous system, or 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. 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, if any.

Successful completion of clinical trials at each applicable stage of development is a prerequisite to submitting an NDA to the FDA or equivalent filings outside the U.S. and, consequently, the ultimate approval and commercial marketing of any of our product candidates for the indications in which we develop them. We do not know whether any of our ongoing 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 one or more clinical trials on full or partial clinical 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 trials; challenges associated with the nature of clinical trial protocols; the availability of existing treatments for the relevant disease; the requirement for in-patient stays with respect to some 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;
- the impact of the COVID-19 pandemic;
- 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. In addition, a clinical trial may be suspended or terminated by us, the FDA or other regulatory authorities, the IRB or Ethics Committee, or EC, at the sites where the IRBs or ECs are overseeing a clinical trial, or recommended for termination or suspension by a data and safety monitoring board, 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. These decisions may increase costs, and cause us not to meet expected timelines and, correspondingly, our business and financial prospects could be adversely affected. 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 from resulting products, if any, 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;
- form relationships with other entities, some of which may be our competitors; or
- be impacted by the COVID-19 pandemic in ways that adversely affect our business.

These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical trials, and may subject us to unexpected cost increases that are beyond our control. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements, and scientific standards, and our reliance on CROs does not relieve us of our regulatory responsibilities. We, clinical investigators, and our CROs are required to comply with regulations and guidelines, including GCPs, for conducting, monitoring, recording and reporting the results of clinical trials to ensure that the data and results are scientifically credible and accurate, and that the trial patients are adequately informed of the potential risks of participating in clinical trials. These regulations are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for any product candidates in clinical development or where clinical trials are being conducted. The FDA enforces GCP regulations through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we or our CROs or clinical investigators or 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, investigators, CROs and contract laboratories comply with GCPs. In addition, our clinical trials must be conducted with product candidates produced under GMPs regulations. If we or our CROs or contract manufacturers fail to comply with these regulations or if the quality or accuracy of the clinical data obtained is compromised due to the failure to adhere to our clinical protocols or other regulatory requirements or for other reasons, and we are unable to rely on clinical data collected, we may be required to repeat clinical trials or extend the duration of, or increase the size of our clinical trials. This would delay the regulatory approval process, and could also subject us to enforcement action up to and including civil and criminal penalties. If any of our relationships with third-party CROs terminate or if a CRO needs to be replaced, we may not be able to enter into arrangements with alternative CROs in a timely manner or at all. Any of these issues could significantly delay or prevent regulatory approval of our product candidates and require significantly greater expenditures. In such an event, we believe that our financial results might be harmed, our costs could increase and our ability to generate revenue from products beyond ZULRESSO could be delayed.

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 also rely on our contract manufacturers to manufacture sufficient quantities of zuranolone, SAGE-324, SAGE-718, SAGE-904 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 long-term supply agreements with our contract manufacturers with respect to ZULRESSO drug substance and drug product. We have an inventory of ZULRESSO drug product and drug substance in place to help mitigate any potential supply risks, but there is no guarantee that this inventory will be adequate. We do not yet have long-term supply agreements in place with our contract manufacturers with respect to drug substance or drug product for any of our product candidates. Each batch of drug substance and drug product for our product candidates is individually contracted through a purchase order governed by our master service and quality agreements. If our existing contract manufacturers for our other product candidates are not willing to enter into long-term supply agreements, or are not willing or are unable to supply drug substance or drug product to us, 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 product(s) or successfully complete development of our current or future product candidates.

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 its 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. Patients who are prescribed medications for the treatment of their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their prescription drugs. There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Regulatory approvals, pricing and reimbursement for new drug products vary widely from country to country. In the U.S., the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare and Medicaid Services, or CMS, an agency within the Department of Health and Human Services, or HHS. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. Commercial third-party payors, such as private health insurers and health maintenance organizations, also decide which medications they will pay for and establish reimbursement levels, though commercial third-party payors often follow CMS' reimbursement determinations. The availability of coverage and the extent of reimbursement by governmental and private payors is essential for most patients to be able to afford treatments. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition. If coverage and adequate reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

Obtaining coverage and reimbursement approval for a product from a government or other third-party payor can be an expensive and time-consuming process that could require us to provide supporting scientific, clinical and cost effectiveness data for the use of our products to the payor. The industry competition to be included in third-party payors' drug formularies, or lists of medications for which third-party payors provide coverage and reimbursement, often leads to downward pricing pressures on pharmaceutical products. In addition, third-party payors may refuse to include a particular branded drug in their formularies or otherwise restrict patient access through formulary controls or otherwise to a branded drug when a less costly generic equivalent or other alternative is available. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors, and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price, or ASP, and best price. Penalties may apply in some cases when such metrics are not submitted accurately and on a timely basis. We cannot be sure that reimbursement will be available for any product candidate that we commercialize and, if reimbursement is available, the level of reimbursement.

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;
- the incidence and severity of any side effects of the products;
- limitations or warnings contained in the labeling approved for our products by the FDA or other applicable regulatory authorities;
- the clinical indications and size of patient populations for which our products are approved;
- 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 settings 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.

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 any future approved products, to the extent permitted, may require significant resources and may never be successful. The resources we dedicate to commercialization of ZULRESSO may not be sufficient to be successful. 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.

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, could result in the need for additional non-clinical studies or 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, or addition of or modification of a REMS;
- 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 products or product candidates; and
- our reputation may suffer.

We believe that any of these events could prevent us from achieving or maintaining market acceptance of the affected products, and could substantially increase the costs of developing our product candidates or commercializing our products and significantly impact our ability to successfully develop and 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 non-clinical studies or clinical trials be completed prior to commencement of such pediatric studies.

As was the case with brexanolone, the FDA may recommend controlled substance scheduling for our current or future product candidates, if approved. 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 manufacturers for our products or product candidates fail to comply with applicable regulatory requirements, a regulatory agency may, among other things:

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

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

Competing therapies may exist or could emerge that adversely affect the amount of revenue we are able to generate from the sale of ZULRESSO 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 products or product candidates or address similar markets. It is probable that the number of companies seeking to develop products and therapies similar to our products 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, zuranolone, is in Phase 3 development for MDD and PPD. Patients with MDD are typically treated with a variety of antidepressant medications, including SSRIs and SNRIs. If successfully developed and approved, zuranolone may also face competition from esketamine, which is approved for the treatment of treatment resistant depression, as well as the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior. A number of companies are developing product candidates intended for the treatment of MDD, including NMDA receptor antagonists or partial antagonists such as dextromethorphan/bupropion, or AXS-05. In July 2020, Axsome Therapeutics, Inc. announced that it had completed a pre-NDA meeting with the FDA for AXS-05 for the treatment of MDD, and that based on the feedback from the FDA, the company remained on track to submit its planned NDA filing for AXS-05 in MDD in the fourth quarter of 2020. In addition, if zuranolone is successfully developed and approved for PPD, it could reduce our commercial opportunity for ZULRESSO.

In the field of neuroactive steroids focused specifically on modulation of GABAA receptors, we also face competition from other companies, including Marinus Pharmaceuticals, Inc. and Praxis Precision Medicines.

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 zuranolone 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 zuranolone, 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. Our collaborators may face competing priorities or different incentives that divert resources away from our collaboration; may independently develop, or develop with a competitor, competitive products; or may believe that product candidates being evaluated in the collaboration could be competitive with the collaborator's own products. In 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 and our existing product candidates or we may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

The success of our business depends upon our ability to successfully develop, gain approval of and commercialize 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 our development efforts related to our current and future product candidates are successful, we may need 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 that may be necessary to potentially commercialize future products, if our development efforts are successful, we may in the future need to increase our number of employees and the scope of our operations. For example, if we are ultimately successful in our development efforts with respect to zuranolone and it is approved as a treatment for MDD, we will need to recruit and train additional qualified personnel, continue to implement and improve our managerial, operational and financial systems, and expand our facilities. In addition, in the event we expand, 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 any expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure and give rise to operational mistakes or delays, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Any 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 any potential expansion, our expenses may increase more than expected, and our ability to successfully develop and gain regulatory approval of our product candidates and generate or increase our revenue, if such product candidates are approved, could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize any future products that we successfully develop, and to compete effectively will depend, in part, on our ability to effectively manage the potential future expansion of our company.

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

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

Recruiting and retaining qualified personnel will 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. If we are unable to continue to attract and retain high quality personnel, our business, financial condition, results of operations and growth prospects could be adversely affected.

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-kickback 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 laws. 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.

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 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 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 Affordable Care Act, or ACA, or otherwise also could affect our 340B ceiling price calculations and negatively impact our results of operations.

The ACA 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 ACA also obligates the Secretary of the HHS to create regulations and processes to improve the integrity of the 340B program. HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that are found to have knowingly and intentionally overcharged covered entities, which became effective on January 1, 2019. 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. The Medicare Part B drug payment methodology is also 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 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 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 Office of the Inspector General of the U.S. Department of Health and Human Services have pursued manufacturers that were alleged to have failed to report these data to the government in a timely manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. We cannot guarantee that our submissions will not be found by CMS to be incomplete or incorrect.

In order to be eligible to have our products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by the Department of Veterans Affairs, or VA, Department of Defense, or DoD, Public Health Service, and Coast Guard, which we refer to as 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, knowingly providing false information in connection with a Non-FAMP filing can subject a manufacturer to penalties 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 (including any kickback, bribe or certain rebate), in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers and formulary managers, among others, on the other. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.
- 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. For example, pharmaceutical companies have been prosecuted under the False Claims Act in connection with their alleged off-label promotion of drugs, purportedly concealing price concessions in the pricing information submitted to the government for government price reporting purposes, and allegedly providing free product to customers with the expectation that the customers would bill federal health care programs for the product. In addition, the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the False Claims Act.
- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. Similar to the federal anti-kickback statute, a person or entity does not need to have actual knowledge of the healthcare fraud statute implemented under HIPAA or specific intent to violate it in order to have committed a violation.
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes privacy, security and breach reporting obligations, including mandatory contractual terms, with respect to safeguarding the privacy and security of individually identifiable health information upon covered entities subject to the rule, such as health plans, healthcare clearinghouses and healthcare providers and their respective business associates and independent contractors that perform certain services for them that involve the use or disclosure of individually identifiable health information on their behalf. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions.
- The federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services.
- The federal transparency requirements, sometimes referred to as the "Sunshine Act", under the ACA, require manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report to HHS information related to physician

payments and other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners.

- Analogous state laws and regulations, such as state anti-kickback and false claims laws and transparency laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures and drug pricing.
- Various federal and state health information and data protection laws and regulations, and similar types of laws outside the U.S., govern the collection, use, disclosure and protection of health-related and other personal information by us and our collaborators.

Ensuring that our future practices and business arrangements comply with applicable healthcare laws and regulations 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.

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

In the event we enroll subjects in our ongoing or future clinical trials in the EU, we may be subject to additional privacy restrictions. The collection, use, storage, transfer, and other processing of personal data, including personal health data, regarding individuals in the European Economic Area is governed by, as of May 25, 2018, the General Data Protection Regulation, or GDPR. The GDPR imposes several requirements on companies that process personal data, including requirements relating to the processing of health data and other sensitive data, the consent of the individuals to whom the personal data relates, the information provided to the individuals regarding data processing activities, the notification of data processing obligations to the competent national data protection authorities, and certain measures to be taken when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data out of the European Economic Area, including to the U.S. Failure to comply with the requirements of the GDPR, and the related national data protection laws of the EU Member States may result in fines and other administrative penalties. The GDPR introduces substantial fines for breaches of the data protection rules. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR includes restrictions on cross-border data transfers. The GDPR regulations may impose additional responsibility and liability in relation to personal data that we process and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules, including as implemented by individual countries. This may be onerous and adversely affect our business, financial condition, results of operations and prospects. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any European activities. Further, the United Kingdom's exiting of the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated.

California recently enacted the California Consumer Privacy Act, or CCPA, which creates new individual privacy rights for California consumers (as defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA will require covered companies to provide certain disclosures to consumers about its data collection, use and sharing practices, and to provide affected California residents with ways to opt-out of certain sales or transfers of personal information. The CCPA went into effect on January 1, 2020, and the California Attorney General is now empowered to commence enforcement actions against violators. While there is currently an exception for protected health information that is subject to HIPAA and clinical trial regulations, as currently written, the CCPA may impact our business activities. The California Attorney General has proposed draft regulations, which have not been finalized to date, that may further impact our business activities if they are adopted. The uncertainty surrounding the implementation of CCPA exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information.

Additionally, HIPAA, as amended by HITECH and its implementing regulations, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," those independent contractors or agents of covered entities that create, receive, maintain, transmit or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The ability of the FDA and other government agencies to review and approve new products in a timely manner could be negatively impacted by a variety of factors, including inadequate funding, which could hinder or 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, the COVID-19 pandemic, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years, and may continue to fluctuate. The FDA and other government agencies may require additional time to review applications for new products beyond the expected timelines, as was the case with ZULRESSO, or may request additional information which could require additional time to review. 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, 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 employees and stop critical activities. If a prolonged government shutdown occurs in the future, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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 entails additional restrictions and may cause delays in commercialization even if a product candidate is approved.

Brexanolone, 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, 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 lengthen the review time prior to marketing of a product candidate, as was the case with ZULRESSO. 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 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 certain 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 products are determined to be controlled substances, the manufacturing, shipping, storing, selling and using of the products will be subject to an additional regulation. Distribution, prescribing and dispensing of these drugs are also regulated.

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 ZULRESSO and any of our product candidates, if successfully developed and approved, is challenging, and may become even more challenging in the future due to, among other reasons, policies advanced by the current and future presidential administrations 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 severity or other criteria more restrictive than the approved label for our product or may limit the amount of reimbursement. These restrictions or limitations might impede appropriate use of our product for the approved indication. Restrictions and limitations on reimbursement or delays in obtaining coverage may vary significantly among payors and payor types. For example, the availability, terms and timing of coverage from state Medicaid systems is expected to vary significantly by state, and we may encounter states that impose significant restrictions or lengthy delays on the reimbursement of our products. Similarly, there are healthcare settings who will not treat Medicaid patients even if they are active sites of care for ZULRESSO. 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 or on the timing 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. For example, Brexit has already and may continue to adversely affect European and/or worldwide regulatory conditions. Brexit could continue to lead to legal uncertainty and potentially divergent national laws and regulations in Europe, including those related to the pricing of prescription pharmaceuticals, as the United Kingdom determines which EU laws to replicate or replace, which could impair our ability to transact business in the EU and the United Kingdom in the future, if we elect to seek regulatory approval and commercialize any of our products there, if approved.

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 zuranolone, 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, or the Regents, and will expire in 2033. We also have an issued U.S. patent covering the formulation of brexanolone i.v., which will expire in 2033. We currently have one issued U.S. patent covering the composition of matter of zuranolone, two issued U.S. patents covering methods of using zuranolone, 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 brexanolone i.v., zuranolone, SAGE-689, SAGE-324, and SAGE-718. We cannot provide any assurances that any of our pending patent applications will mature into issued patents. For example, the U.S. Patent and Trademark Office, or U.S. PTO, has issued a final rejection against one of our patent applications claiming a proprietary GABAA positive allosteric modulator compound, asserting a lack of novelty and non-obviousness. We are in the process of appealing this decision to the Patent Trial and Appeal Board. We may be unable to obtain issued patents covering our proprietary compounds. We cannot provide any assurances that any of our issued patents will be enforceable or include, claims with a scope sufficient to protect our product candidates or otherwise provide any competitive advantage. For example, the issued patent and patent applications that provide coverage for ZULRESSO only cover particular formulations and particular methods of using such formulations to treat depressive disorders such as PPD and MDD. As a result, such issued patent and any patent that may issue from such patent applications, would not prevent third-party competitors from creating, making and marketing alternative formulations of brexanolone that fall outside the scope of the patent claims or 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. For example, our granted European patent covering brexanolone i.v. has been opposed by a third party, and the opposition proceedings are ongoing. Thus, any patents, should they issue, that we may own or exclusively license may not provide any protection against competitors. Furthermore, an adverse decision in an interference proceeding 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 ZULRESSO and our other product candidates, if approved.

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

The pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may allege that our product candidates or the use of our technologies infringes patent claims or other intellectual property rights held by them or that we are employing their proprietary technology without authorization. As we continue to develop 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. 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. For example, our granted European patent covering brexanolone i.v. has been opposed by a third party, and the opposition proceedings are ongoing. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on 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 2020 report from the Office of the U.S. Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. This could make it difficult for us to stop the infringement of our patents, if obtained, or the misappropriation of our other intellectual property rights in such jurisdictions. 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 approved. If we breach any of the agreements under which we license the use, development and commercialization rights to our product candidates or technology from third parties or, in certain cases, we fail to meet certain development deadlines, we could lose license rights that are important to our business.

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

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

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

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

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

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

With respect to our proprietary formulation of brexanolone, we have entered into an exclusive license agreement with CyDex Pharmaceuticals, Inc., or CyDex, a wholly owned subsidiary of Ligand Pharmaceuticals, Inc., to use its Captisol technology to develop brexanolone for the field of use, which includes all fields for the treatment, prevention or diagnosis of any disease or symptom in humans or animals other than (i) the ocular treatment of any disease or condition with a formulation, including a hormone; (ii) topical ocular treatment of inflammatory conditions; (iii) treatment and prophylaxis of fungal infections in humans; and (iv) any ocular treatment for retinal degeneration. We are obligated to pay CyDex certain clinical and regulatory milestones and 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 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 product candidates as a result of such funding, intellectual property rights to such discoveries may be subject to the applicable provisions of the Bayh-Dole Act.

If we do not obtain new chemical entity or other types of marketing and data exclusivity for our product candidates and if we do not obtain additional protection under the 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 U.S. Supreme Court held that several claims drawn to measuring drug metabolite levels from patient samples and correlating them to drug doses were not patentable subject matter. The decision appears to impact diagnostics patents that merely apply a law of nature via a series of routine steps and it has created uncertainty around the ability to obtain patent protection for certain inventions. Additionally, on June 13, 2013 in *Association for*

Molecular Pathology v. Myriad Genetics, Inc., the U.S. Supreme Court held that claims to isolated genomic DNA are not patentable, but claims to complementary DNA molecules are patent eligible because they are not a natural product. 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 U.S. Supreme Court held that the patent eligibility of claims directed to abstract ideas, products of nature, and laws of nature should be determined using the same framework set forth in *Prometheus*. The U.S. PTO 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 issued, 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 Industry-Related Risks

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% (pursuant to the Bipartisan Budget Act of 2018, effective as of 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer’s outpatient drugs to be covered under Medicare Part D.

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. On December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional and remanded the case to the lower court to reconsider its earlier invalidation of the full ACA. The U.S. Supreme Court has scheduled oral arguments for the case on November 10, 2020. On June 25, 2020, the Trump Administration and a coalition of 18 states asked the U.S. Supreme Court to strike down the entirety of the ACA. Pending review, the ACA remains in effect, but it remains unclear how such litigation and other efforts to repeal and replace the ACA will impact the ACA and our business. Litigation and legislation with respect to the ACA are likely to continue, with unpredictable and uncertain results.

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. On April 27, 2020, the U.S. Supreme Court reversed this decision.

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; however, on December 20, 2019, the President signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repeals the Cadillac tax, the health insurance provider tax, and the medical device excise tax. 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 gives 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 U.S. 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 2029 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 U.S. 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 2020 contains further drug price control measures that could be enacted during the 2020 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. 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 May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. Congress and the current administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on September 25, 2019, the Senate Finance Committee introduced the Prescription Drug Pricing Reduction Action of 2019, a bill intended to reduce Medicare and Medicaid prescription drug prices. The proposed legislation would restructure the Part D benefit, modify payment methodologies for certain drugs, and impose an inflation cap on drug price increases. An even more restrictive bill, the Lower Drug Costs Now Act of 2019, has passed out of the House and was delivered to the Senate on December 16, 2019. It would require CMS to directly negotiate drug prices with manufacturers and these prices must be offered under Medicare Part B and Part D. Specifically, as the bill is currently written, the negotiated maximum price may not exceed 120 percent of the average price in Australia, Canada, France, Germany, Japan, and the United Kingdom or, if such information is not available, 85 percent of the U.S. average manufacturer price. It is unclear whether either of these bills will make it through both chambers and be signed into law, and if either is enacted, what effect it could have on our business. 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 or on the timing 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, including as a result of the COVID-19 pandemic, 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, including as a result of the COVID-19 pandemic, 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, pandemic 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 could be required to expend significant amounts of money and other resources to respond to these threats or breaches and to repair or replace information systems or networks. We also could suffer financial loss or the loss of valuable confidential information. In addition, we could be subject to regulatory actions and/or claims made by individuals and groups in private litigation involving privacy issues related to data collection and use practices and other data privacy laws and regulations, including claims for misuse or inappropriate disclosure of data, as well as unfair or deceptive practices. Although we develop and maintain systems and controls designed to prevent these events from occurring and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes are costly and require ongoing monitoring and updating as technologies change and efforts to overcome security measures become increasingly sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely and there can be no assurance that any measures we take will prevent cyber-attacks or security breaches that could adversely affect our business.

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

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

Risks Related to Our Financial Position and Need for Capital

We are a biopharmaceutical company with a limited operating history, and have not generated significant revenue to date. 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 September 30, 2020, we had received net proceeds of $2.2 billion from such transactions. As of September 30, 2020, our cash, cash equivalents and marketable securities were $668.5 million. We have incurred significant net losses in each year since our inception, including net losses of $368.8 million for the nine months ended September 30, 2020 and $680.2 million for the year ended December 31, 2019, and our accumulated deficit was $2.0 billion as of September 30, 2020. Substantially all of our operating losses have resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. We expect to incur increasing levels of operating losses over the next several years and for the foreseeable future. Our prior losses, combined with expected future losses, have had, and will continue to have, an adverse effect on our stockholders' equity and working capital. We expect our research and development expenses 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 incur significant selling, general and administrative costs in support of ongoing commercialization efforts with respect to ZULRESSO. In addition, if we obtain marketing approval for our current or 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 any future approved product depends on a number of factors, including, but not limited to:

- our ability to initiate and successfully complete all efficacy and safety clinical trials and non-clinical studies required to file for, and obtain, U.S. and foreign marketing approval for our product candidates; and our ability to file for and receive marketing approval to commercialize our product candidates, if successfully developed; and
- 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 and satisfactory reimbursement of such product in the medical community, with patients and with third-party payors.

In April 2020, we implemented a workforce reduction that primarily affected the ZULRESSO commercial operation and related support functions, including eliminating the entire salesforce. While we remain committed to working with healthcare providers and women with PPD seeking access to ZULRESSO, our ongoing commercial efforts, including our small account management field-based team, are primarily focused on geographies that have existing, active ZULRESSO treating sites. We expect that this approach to our commercial efforts may continue to substantially limit the revenue opportunity for ZULRESSO. The rapid spread of COVID-19 in the U.S. has had a negative impact on our revenue from sales of ZULRESSO. A number of states within the U.S. are seeing a resurgence of cases of COVID-19 after beginning to reopen businesses and public facilities, and these surges could continue or worsen as states lift restrictions, which could further negatively impact our revenue from sales of ZULRESSO. We expect to continue to incur significant 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 expenses to increase substantially as we continue to advance our product candidates in clinical trials, continue our discovery efforts and seek regulatory approval of our product candidates, if we generate positive data in our other clinical programs. We also continue to incur significant expenses in connection with the commercialization of ZULRESSO and would expect commercialization expenses to increase significantly to commercialize other products, if successfully developed and approved. We also expect to require additional capital in the future 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, conduct additional clinical trials for indications we are already pursuing beyond the anticipated trials, identify new potential opportunities or otherwise expand our activities more rapidly than we presently anticipate.

As of September 30, 2020, our cash, cash equivalents and marketable securities were $668.5 million. Based on our current operating plans, we expect that our existing cash, cash equivalents and marketable securities will be sufficient to fund our anticipated level of operations into 2022. 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 for, obtain regulatory approval for, and to commercialize our product candidates. Raising funds in the current economic environment may present additional challenges. The COVID-19 pandemic has caused major volatility in the stock market and a significant global economic downturn. If the pandemic and related economic downturn continue for an extended period or surges in the number of cases of COVID-19 continue or worsen in the future, or if our business prospects are impaired or the capital markets disrupted for any other reason, additional capital may not be available to us on acceptable terms, or at all. Failure to obtain this capital when needed may force us to delay, limit or terminate our product development efforts or other operations. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or in light of other strategic considerations.

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 and potentially more dilutive to our existing stockholders. For example, after the announcement of the topline results of the Phase 3 MOUNTAIN Study of zuranolone on December 5, 2019, our stock price declined significantly and has remained significantly lower than it had been prior to the results announcement. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders. The issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

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.

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.

Changes in tax laws may adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, local and foreign income taxation are continuously under review by legislators and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. For example, in March 2020, President Trump signed into law the Families First Coronavirus Response Act, or the FFCR Act, and the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, which included certain changes in tax law intended to stimulate the U.S. economy in light of the COVID-19 pandemic, including temporary beneficial changes to the treatment of net operating losses, interest deductibility limitations and payroll tax matters. Regulatory guidance under the FFCR Act, the CARES Act and other recent legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen impact of these laws on our business and financial condition. It is also possible that Congress will enact additional legislation in connection with the COVID-19 pandemic, some of which could have an impact on our company. In addition, it is uncertain if and to what extent various states will conform to the FFCR Act, the CARES Act, or the TCJA.

Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations. We urge investors to consult with their legal and tax advisers regarding the implications of potential changes in tax laws on an investment in our common stock.

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

As of December 31, 2019, we had federal and state net operating loss carryforwards of $1.4 billion and $1.0 billion, respectively, which begin to expire in 2031 and 2030, respectively (other than federal net operating loss carryforwards generated in taxable years beginning after December 31, 2017, which are not subject to expiration). As of December 31, 2019, we also had federal and state research and development tax credit carryforwards of $34.2 million and $7.4 million, respectively, which begin to expire in 2031 and 2027, respectively. As of December 31, 2019, we had federal orphan drug tax credit carryforwards of $40.0 million, which begin to expire in 2034. Under Section 382 of the Internal Revenue Code of 1986, as amended, 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.

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 zuranolone 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;
- the impact of the COVID-19 pandemic;
- announcements of new products, technologies, commercial relationships, acquisitions, collaborations 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;
- the state of the U.S. and world economies, general market conditions and overall fluctuations in U.S. equity markets, including as a result of U.S. or world events;
- changes in healthcare laws affecting pricing, reimbursement or access;
- variations in our quarterly operating results;
- changes in our financial guidance or securities analysts’ estimates of our financial performance;
- changes in accounting principles;
- our ability to raise additional capital and the terms on which we can raise it;
- 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 our existing cash and the proceeds from our past and potential future follow-on public offerings, and may not use such cash and proceeds effectively, which could affect our results of operations and cause our stock price to decline.

We have considerable discretion in the use of our cash and the application of the net proceeds from our follow-on public offerings. We may use cash and net proceeds for purposes that do not yield a significant return or any return at all for our stockholders. In addition, pending their use, we may invest the net proceeds from 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
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.INS*	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document)
101.SCH*	Inline XBRL Taxonomy Extension Schema Document
101.CAL*	Inline XBRL Taxonomy Extension Calculation Database Document
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104*	Cover Page Interactive Data File (formatted as inline XBRL 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.

November 5, 2020

By: /s/ Jeffrey M. Jonas
Jeffrey M. Jonas, M.D.
Chief Executive Officer, President and Director
(Principal Executive Officer)

November 5, 2020

By: /s/ Kimi Iguchi
Kimi Iguchi
Chief Financial Officer
(Principal Financial and Accounting Officer)

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 September 30, 2020 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 control 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: November 5, 2020

/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 September 30, 2020 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 control 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: November 5, 2020

/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 September 30, 2020, 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: November 5, 2020

/s/ Kimi Iguchi
Name: Kimi Iguchi
Title: Chief Financial Officer (Principal Financial and
Accounting Officer)
Date: November 5, 2020