UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2018

OR

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

For the transition period from _____ to _____

Commission File Number 001-37635

AXSOME THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**45-4241907**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
25 Broadway 9th Floor New York, New York	**10004**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: (212) 332-3241

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

Common Stock, Par Value $0.0001 Per Share	Nasdaq Global Market
(Title of Class)	(Name of Each Exchange on Which Registered)

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

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.
Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act.
Yes ☐ No ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filed, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" , and "emerging growth company" in Rule 12b-2 of the Exchange Act). (Check one):

Large accelerated filer ☐	Accelerated filer ☒
Non-accelerated filer ☐	Smaller reporting company ☒
	Emerging growth company ☒

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of voting common stock held by non-affiliates of the registrant (assuming for purposes of this calculation, without conceding, that all executive officers and directors are "affiliates") was approximately $58.1 million as of June 30, 2018, based on the closing sale price of such stock as reported on the Nasdaq Global Market.

There were 33,280,355 shares of the registrant's common stock outstanding as of March 11, 2019.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2019 Annual Meeting of Stockholders (the "Proxy Statement"), to be filed within 120 days of the registrant's fiscal year ended December 31, 2018, are incorporated by reference in Part III of this Annual Report on Form 10-K. Except with respect to information specifically incorporated by reference in this Annual Report on Form 10-K, the Proxy Statement is not deemed to be filed as part of this Annual Report on Form 10-K.

AXSOME THERAPEUTICS, INC.
ANNUAL REPORT ON FORM 10-K
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2018

TABLE OF CONTENTS

CAUTIONARY NOTE

REGARDING FORWARD-LOOKING STATEMENTS

Certain matters discussed in this report, including matters discussed under the caption “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” may constitute forward-looking statements for purposes of the Securities Act of 1933, as amended, or the Securities Act, and the Securities Exchange Act of 1934, as amended, or the Exchange Act, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from the future results, performance or achievements expressed or implied by such forward-looking statements. The words "anticipate," "believe," "estimate," "may," "expect" and similar expressions are generally intended to identify forward-looking statements. Our actual results may differ materially from the results anticipated in these forward-looking statements due to a variety of factors, including, without limitation, those discussed under the captions “Risk Factors,” “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and elsewhere in this report, as well as other factors which may be identified from time to time in our other filings with the Securities and Exchange Commission, or the SEC, or in the documents where such forward-looking statements appear. All written or oral forward-looking statements attributable to us are expressly qualified in their entirety by these cautionary statements. Such forward-looking statements include, but are not limited to, statements about our:

- expectations for increases or decreases in expenses;
- expectations for the clinical and preclinical development, manufacturing, regulatory approval, and commercialization of our pharmaceutical product candidates or any other products that we may acquire or in-license;
- estimates of the sufficiency of our existing capital resources combined with future anticipated cash flows to finance our operating requirements;
- expectations for incurring capital expenditures to expand our research and development and manufacturing capabilities;
- expectations for generating revenue or becoming profitable on a sustained basis;
- expectations or ability to enter into marketing and other partnership agreements;
- expectations or ability to enter into product acquisition and in-licensing transactions;
- expectations or ability to build our own commercial infrastructure to manufacture, market and sell our product candidates;
- expected losses;
- ability to obtain and maintain intellectual property protection for our product candidates;
- acceptance of our products by doctors, patients, or payors;
- stock price and its volatility;
- ability to attract and retain key personnel;
- the performance of third-party manufacturers;
- expectations for future capital requirements; and
- our ability to successfully implement our strategy.

The forward-looking statements contained in this report reflect our views and assumptions only as of the date that this report is signed. Except as required by law, we assume no responsibility for updating any forward-looking statements.

We qualify all of our forward-looking statements by these cautionary statements. In addition, with respect to all of our forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

PART I

Unless the context requires otherwise, references in this report to "Axsome," "Company," "we," "us" and "our" and similar designations refer to Axsome Therapeutics, Inc. and our subsidiaries.

ITEM 1. BUSINESS.

OVERVIEW

We are a clinical-stage biopharmaceutical company developing novel therapies for the management of central nervous system, or CNS, disorders for which there are limited treatment options. By focusing on this therapeutic area, we are addressing significant and growing markets where current treatment options are limited or inadequate. Our core CNS portfolio includes four CNS product candidates, AXS-05, AXS-07, AXS-09, and AXS-12, which are being developed for multiple indications. We are conducting a Phase 3 trial with AXS-05 in treatment resistant depression, or TRD, which we refer to as the STRIDE-1 study, a Phase 2/3 trial in agitation associated with Alzheimer's disease, or AD, which we refer to as the ADVANCE-1 study. Additionally, AXS-05 is currently in a Phase 2 trial in smoking cessation and we recently completed a Phase 2 trial in major depressive disorder, or MDD, which we refer to as the ASCEND study. AXS-05 met the prespecified primary endpoint and significantly improved symptoms of depression in the ASCEND trial. We are conducting a Phase 3 trial with AXS-07 in the acute treatment of migraine, pursuant to a U.S. Food and Drug Administration, or FDA, Special Protocol Assessment, or SPA. We are conducting a Phase 2 trial with AXS-12 in narcolepsy. Additionally, we are currently evaluating other product candidates, which we intend to develop for CNS disorders. We aim to become a fully integrated biopharmaceutical company that develops and commercializes differentiated therapies that expand the treatment options available to caregivers and improve the lives of patients living with CNS disorders.

AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity under development for the treatment of CNS disorders. AXS-05 consists of bupropion and dextromethorphan, or DM, and utilizes our metabolic inhibition technology. We are developing AXS-05 initially for the following four indications: TRD, agitation associated with AD, MDD, and as an aid to smoking cessation. The DM component of AXS-05 is a non-competitive N-methyl-D-aspartate, or NMDA, receptor antagonist, also known as a glutamate receptor modulator. The DM component of AXS-05 is also a sigma-1 receptor agonist, nicotinic acetylcholine receptor antagonist, and inhibitor of the serotonin and norepinephrine transporters. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. We intend to seek FDA approval for AXS-05 utilizing the 505(b)(2) regulatory development pathway.

AXS-07 is a novel, oral, investigational medicine consisting of MoSEIC™, or Molecular Solubility Enhanced Inclusion Complex, meloxicam and rizatriptan. We are developing AXS-07 initially for the acute treatment of migraine. Meloxicam is a long-acting nonsteroidal anti-inflammatory drug, or NSAID, with COX-2, an enzyme involved in inflammation and pain pathways, preferential inhibition and potent pain-relieving effects. However, standard meloxicam has an extended time to maximum plasma concentration, or T_{max}, which delays its onset of action. AXS-07 utilizes our proprietary MoSEIC™ technology to substantially increase the solubility and speed the absorption of meloxicam while potentially maintaining durability of action. Meloxicam is a new molecular entity for migraine enabled by our MoSEIC™ technology. Rizatriptan is a 5-$HT1_{B/D}$ agonist that inhibits calcitonin gene-related peptide (CGRP)-mediated vasodilation, has been shown to have central trigeminal antinociceptive activity, and may reduce the release of inflammatory mediators from trigeminal nerves. Rizatriptan is approved as a single agent for the acute treatment of migraine. We intend to seek FDA approval for AXS-07 utilizing the 505(b)(2) regulatory development pathway.

AXS-09 is an oral, investigational medicine consisting of esbupropion and DM, which is being developed for the treatment of CNS disorders. AXS-09 contains esbupropion, the chirally pure S-enantiomer of bupropion, as compared to the company's first generation product candidate AXS-05 which contains racemic bupropion, equal amounts of the S- and R-enantiomers. We have demonstrated in a Phase 1 trial that DM plasma levels are substantially increased into a potentially therapeutic range with repeated administration of AXS-09. Results of this Phase 1 trial coupled with preclinical data also indicate the potential for enhanced absorption and therapeutic effect of the S-enantiomer as compared to the R-enantiomer.

AXS-12, reboxetine, is a novel, oral, investigational medicine in development for the treatment of narcolepsy. AXS-12 is a highly selective and potent norepinephrine reuptake inhibitor. The potential utility of AXS-12 in narcolepsy is supported by positive pre-clinical and preliminary clinical results in narcolepsy, and an extensive clinical safety record. Reboxetine, the active agent in AXS-12, significantly and dose-dependently reduced narcoleptic episodes in hypocretin (orexin)-deficient mice, a well-established genetic animal model of narcolepsy. AXS-12 has been granted Orphan Drug Designation by the FDA for the treatment of narcolepsy.

The Axsome Pain and Primary Care business unit, or Axsome PPC, houses our pain and primary care assets, including AXS-02 and AXS-06, and intellectual property which covers these and related product candidates and molecules being developed by us and others. AXS-02 is being developed for the treatment of knee osteoarthritis, or OA, associated with bone marrow lesions, or BMLs, and chronic low back pain, or CLBP, associated with Modic changes, or MCs. Lastly, AXS-06 is being developed for the treatment of osteoarthritis and rheumatoid arthritis and for the reduction of the risk of NSAID-associated gastrointestinal ulcers.

AXS-02, disodium zoledronate tetrahydrate, is a potentially first-in-class, oral, targeted, non-opioid therapeutic for chronic pain. AXS-02 is a potent inhibitor of osteoclasts, which are bone remodeling cells that break down bone tissue. We are developing AXS-02 for the treatment of pain in the following two conditions: knee OA associated with BMLs and CLBP associated with type 1 or mixed type 1 and type 2 MCs. These conditions exhibit target lesions or specific pathology that we believe may be addressed by the mechanisms of action of AXS-02, such as inhibition of osteoclast activity. These mechanisms may result in a reduction of pain in these conditions. We intend to seek FDA approval for AXS-02 utilizing the 505(b)(2) regulatory development pathway.

AXS-06 is a novel, oral, non-opioid, investigational medicine consisting of MoSEIC™ meloxicam and esomeprazole. We are developing AXS-06 initially for the treatment of osteoarthritis and rheumatoid arthritis. Esomeprazole is a proton pump inhibitor which lowers stomach acidity and which has been shown to reduce the occurrence of NSAID-associated gastrointestinal ulcers. AXS-06 is designed to provide rapid, effective pain relief, and to reduce the risk of NSAID-associated gastrointestinalulcers, with convenient once-daily dosing. We have successfully completed a Phase 1 trial of AXS-06 to characterize the pharmacokinetics of meloxicam and esomeprazole after oral administration of AXS-06. The results of our Phase 1 trial demonstrated that the median T_{max} for meloxicam, the trial's primary endpoint, was nine times faster for AXS-06 as compared to standard meloxicam. We intend to seek FDA approval for AXS-06 utilizing the 505(b)(2) regulatory development pathway.

Our product candidates are protected through a combination of patents, trade secrets, and proprietary know-how. If approved, they may also be eligible for periods of regulatory exclusivity. Our intellectual property portfolio includes U.S. patents with claims extending to 2034 for AXS-05 and AXS-02 and to 2036 for AXS-07 and AXS-06, as well as corresponding foreign patent applications.

Our Strategy

Our goal is to efficiently develop and commercialize novel, differentiated therapies for the management of CNS disorders. The primary elements of our strategy to achieve this goal are the following:

- ***Pursue novel CNS indications with high unmet medical need.*** We believe that CNS disorders are significantly underserved therapeutic segments with currently limited treatment options. We are initially developing our product candidates for indications that have no or few FDA-approved pharmacological treatments. For example, there currently is no drug approved by the FDA or the EMA for agitation associated with Alzheimer's disease. There are currently only two FDA-approved drugs for TRD. These conditions are often disabling, difficult to treat, and associated with significant comorbidities. By focusing on novel indications, we aim to develop products that have the potential to change current medical practice, and that are highly relevant to patients, physicians, and regulatory bodies because they address unmet medical needs. Many of these indications have significant patient populations which, when combined with the lack or paucity of approved treatments, should provide us with attractive commercial opportunities.

- ***Develop products with our proprietary medicinal chemistry and formulation technologies.*** Our proprietary medicinal chemistry and formulation technologies allow us to continue to design new and innovative medicines to treat CNS conditions. These technologies and capabilities include: (1) chiral chemistry and formulation to identify, isolate and stabilize chirally pure enantiomers, (2) metabolic inhibition as a novel drug delivery method to increase the bioavailability and prolong the half-life of target drug molecules, (3) the MoSEIC™ technology which is designed to substantially increase the solubility and speed the absorption of target drug molecules, and (4) proprietary chemical synthesis and analysis to increase the solubility and enable the oral delivery of target drug molecules.

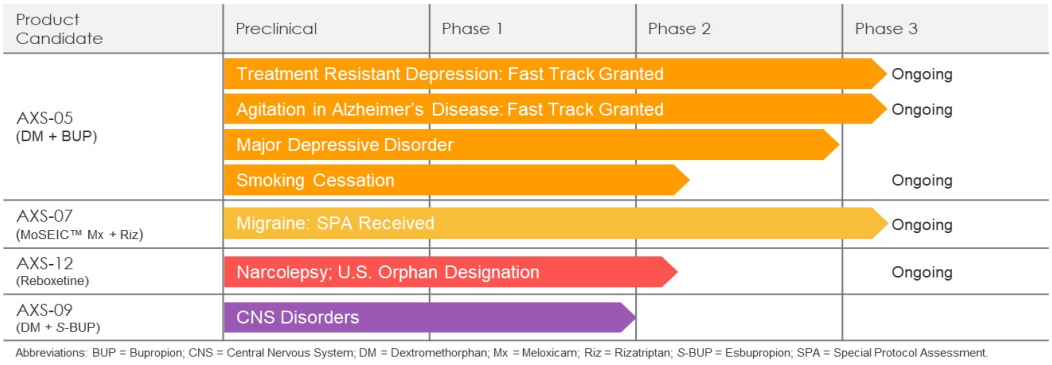
- ***Develop products with differentiated profiles.*** We aim to develop products with novel mechanisms of action for the intended indications that may yield differentiated product profiles. For example, AXS-05 and AXS-09 combine several mechanisms of action resulting in a unique pharmacological profile that may be relevant to the treatment of numerous CNS disorders. The MoSEIC™ technology is designed to improve the absorption of drug molecules after oral administration and is utilized in our AXS-06 and AXS-07 product candidates. AXS-02 utilizes a potentially first-in-class mechanism of action for the treatment of pain that may result in analgesia that lasts for one or more months after treatment. We believe that products with clearly differentiated features will be attractive to patients and their physicians, and will provide us with a competitive commercial advantage.

- ***Use biomarkers to define specific patient subsets for our pain indications.*** We are using biomarkers, such as BMLs and MCs, which are visible on magnetic resonance imaging, or MRI, to define specific subsets of patients who we believe are more likely to respond to the mechanisms of action of AXS-02. Biomarkers have been used successfully in connection with oncology treatments, but are not commonly used with pain therapeutics. While patients with common pain conditions, such as knee OA and CLBP, experience similar symptoms, these symptoms may be due to different underlying conditions. We believe that the variability in underlying conditions contributes to heterogeneity in these populations and may account for observed differences in treatment response. We believe that our targeted biomarker approach may result in a less heterogeneous patient population in our clinical trials, which may improve our ability to demonstrate a treatment effect and, if approved, enable treatment of more appropriate patient populations with our product candidates.

- ***Reduce clinical and regulatory risk, limit development costs, and accelerate time to market.*** Our product candidates incorporate chemical entities with long histories of clinical use and well-characterized safety profiles. Use of well-characterized molecules has allowed us to rapidly complete early clinical development of our product candidates, and may reduce the risk of late-stage clinical failures due to unexpected toxicities. This strategy also allows us to seek FDA approval for some of our product candidates using the 505(b)(2) regulatory pathway. Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, or FDCA, permits an applicant to file a new drug application, or NDA, that relies, in part, on the FDA's prior findings of safety and efficacy in the approval of a similar drug, or on published literature. It therefore allows us to leverage previous preclinical and clinical experience with the active molecules in some of our product candidates and potentially forego conducting certain lengthy and costly preclinical studies, reduce clinical and regulatory risk, limit development costs, and accelerate our time to commercialization.

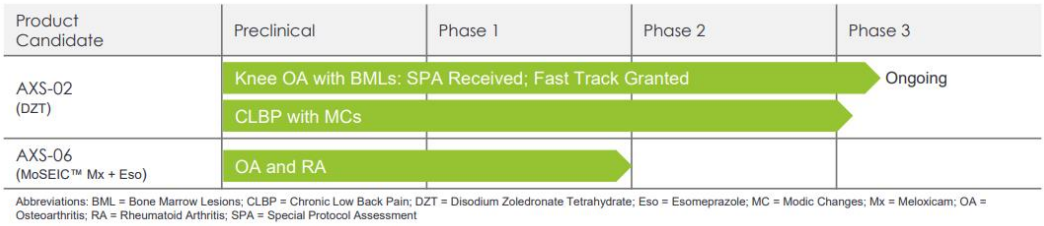
- ***Retain commercial rights in the United States, where appropriate, and selectively partner outside of the United States to maximize the value of our product candidates.*** We intend to commercialize our product candidates, if approved, in the United States through the establishment of our own focused, cost-effective sales and marketing organization targeting high-prescribing specialists. We intend to selectively partner commercial rights outside of the United States with third parties to maximize the value of our product candidates without the substantial investment required to develop independent sales forces in those geographies. We continue to evaluate strategic options for the commercialization of our other product candidates.

Our current CNS product candidate pipeline is summarized in the table below:



Abbreviations: BUP = Bupropion; CNS = Central Nervous System; DM = Dextromethorphan; Mx = Meloxicam; Riz = Rizatriptan; *S*-BUP = Esbupropion; SPA = Special Protocol Assessment.

Additionally, our PPC product candidate pipeline is summarized in the table below:



Abbreviations: BML = Bone Marrow Lesions; CLBP = Chronic Low Back Pain; DZT = Disodium Zoledronate Tetrahydrate; Eso = Esomeprazole; MC = Modic Changes; Mx = Meloxicam; OA = Osteoarthritis; RA = Rheumatoid Arthritis; SPA = Special Protocol Assessment

CNS Product Candidates

AXS-05

Overview

AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity under development for the treatment of CNS disorders. AXS-05 consists of dextromethorphan, or DM, and bupropion and utilizes Axsome's metabolic inhibition technology. The DM component of AXS-05 is a non-competitive N-methyl-D-aspartate, or NMDA, receptor antagonist, also known as a glutamate receptor modulator. The DM component of AXS-05 is also a sigma-1 receptor agonist, nicotinic acetylcholine receptor antagonist, and inhibitor of the serotonin and norepinephrine transporters. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist.

AXS-05 is potentially applicable to the treatment of a variety of CNS disorders, based on the mechanisms of action of its two components. We are developing AXS-05 initially as a therapeutic for treatment resistant depression, or TRD, agitation associated with Alzheimer's disease, or AD, major depressive disorder, or MDD, and as an aid to smoking cessation.

Scientific Rationale

DM and bupropion each target different CNS receptor systems that are potentially relevant to the treatment of CNS disorders. Combining the distinct and independent mechanisms of action of these two compounds may be additive or synergistic in the treatment of depression and other CNS disorders. However, DM is quickly eliminated from the body following administration due to extensive first pass metabolism, which results in low blood levels even at high doses. Attainment of potential therapeutic plasma levels of DM is therefore difficult when DM is dosed as a single agent. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan. This positive pharmacokinetic interaction between bupropion and DM therefore may enable DM's clinical utility by increasing DM's plasma levels into a potentially therapeutic range. We believe this dual pharmacodynamic and pharmacokinetic synergy results in a unique pharmacological profile that could potentially be efficacious in CNS disorders.

Bupropion is a well-characterized antidepressant that is chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitor, or other known antidepressant agents. It is an inhibitor of the neuronal uptake of norepinephrine and dopamine, and does not inhibit monoamine oxidase or the reuptake of serotonin. It is the only antidepressant currently available that is capable of selectively inhibiting both dopamine and norepinephrine reuptake. Bupropion was approved in the United States in 1985 and is marketed under the trade name Wellbutrin for the treatment of major depressive disorder, or MDD, and under the trade name Zyban as an aid to smoking cessation.

DM is a noncompetitive N-methyl-D-aspartate, or NMDA, receptor antagonist, a sigma-1 receptor agonist, and an inhibitor of the serotonin transporter, or SERT, and norepinephrine transporter, or NET. Each of these mechanisms of action has been shown to be associated with antidepressant response. DM is a well-known agent that is used as an antitussive.

Depression

We are developing AXS-05 for the treatment of major depressive disorder, or MDD, and treatment resistant depression, or TRD. We believe there is a substantial need for new effective treatments for this large underserved patient population.

Indication Overview

MDD is a debilitating, chronic, biologically-based disorder characterized by low mood, inability to feel pleasure, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms, and which impairs social, occupational, educational, or other important functioning. In severe cases, MDD can result in suicide. According to the National Institutes of Health, an estimated 6.7% of U.S. adults, or approximately 16 million, experience MDD each year.

Patients diagnosed with MDD are defined as having TRD if they have failed two or more antidepressant therapies. MDD is a serious condition characterized by depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two-week period, and which impairs social, occupational, educational, or other important functioning. MDD is highly prevalent and difficult to treat. According to the National Institutes of Health, or NIH, an estimated 6.7% of U.S. adults experience MDD each year, while 3.3% of individuals 13 to 18 years of age experience a seriously debilitating depressive disorder. Results of the Sequenced Treatment Alternatives to Relieve Depression, or STAR*D trial, funded by the National Institute of Mental Health, indicate that nearly two-thirds of diagnosed and treated patients do not experience adequate treatment response with first-line therapy, and that the majority of these initial failures also fail second-line treatment. Based on these observations, we estimate that there are approximately 3 million patients with TRD in the United States.

Rationale for the Use of AXS-05 in Depression

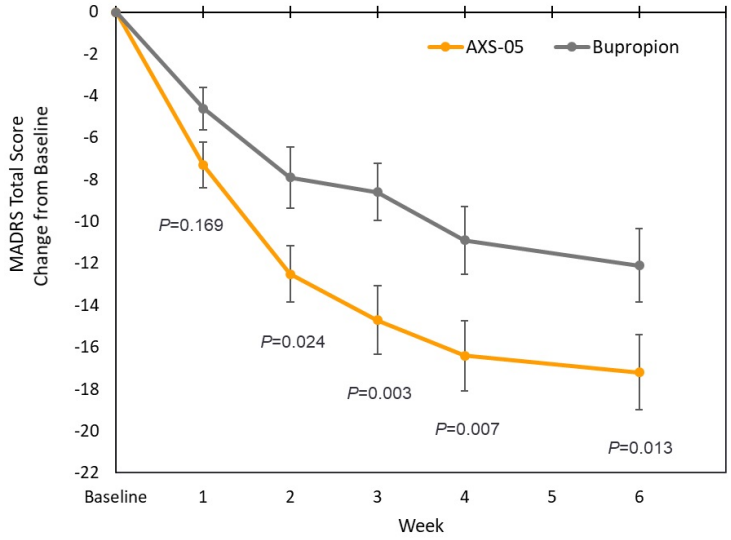
The rationale for the use of AXS-05 in the treatment of depression is based on clinical evidence of antidepressant effects of AXS-05, the mechanisms of action of the DM component of AXS-05, preclinical evidence of antidepressant effects of DM, and the established clinical efficacy of the bupropion component of AXS-05 in MDD.

Mechanistic rationale. DM's mechanisms of action encompass those of several currently marketed antidepressant drugs such as duloxetine (Cymbalta), fluoxetine (Prozac), and fluvoxamine (Luvox). Bupropion inhibits the reuptake of dopamine and is a nicotinic acetylocholine receptor antagonist. The distinct mechanisms of action of DM and bupropion may therefore be complementary. Additionally, we believe that, if successfully developed, the NMDA receptor antagonist properties of DM in AXS-05 may potentially result in a faster onset of action than currently available antidepressant treatments.

Preclinical rationale. The effects of DM have been reported in two preclinical models of antidepressant effect. In the forced swim test model in mice, DM administered intraperitoneally resulted in antidepressant-like effects in a dose-dependent manner. The forced swim test is considered to be the most well-validated animal model for predicting antidepressant effect. Using the tail suspension test in mice, another widely used behavioral test for assessing antidepressant potential, DM was also shown to display antidepressant-like effects similar to those seen with imipramine, a conventional antidepressant, and ketamine, a compound that has demonstrated fast-acting antidepressant effects. In both models, inhibition of DM metabolism using quinidine was shown to potentiate the antidepressant-like effects.

Clinical Rationale. Administration of AXS-05 in the ASCEND study, a Phase 2, randomized, double-blind, active-controlled, multi-center, U.S. trial, resulted a in highly statistically significant reduction in the Montgomery-Åsberg Depression Rating Scale, or MADRS, total score, averaged over the 6-week treatment period, the overall treatment effect, as compared to bupropion ($p<0.001$). At Week 6, AXS-05 demonstrated a 17.2 point reduction in the MADRS total score compared to a 12.1 point reduction for bupropion ($p=0.013$). AXS-05 rapidly reduced depressive symptoms and was superior to bupropion on multiple prespecified secondary endpoints, with statistically significant effects demonstrated on most. Additionally, the treatment effect observed with bupropion in the study was consistent with that observed in prior published trials.

Depressive symptom change with AXS-05 in patients with MDD in the ASCEND Phase 2 trial



	AXS-05	Bupropion	P-Value
Primary Endpoint			
Change in MADRS Total Score over 6-Week Period (averaged)	-13.7	-8.8	< 0.001
Change in MADRS Total Score at Week 6	-17.2	-12.1	0.013

Agitation associated with Alzheimer's Disease (AD)

We are developing AXS-05 for the treatment of agitation associated with AD. There is currently no FDA-approved pharmacological treatment for the indication of agitation associated with AD.

Indication Overview

AD is a progressive neurodegenerative disorder that manifests initially as forgetfulness advancing to severe cognitive impairment and memory loss. It is a common form of dementia and afflicts an estimated 5 million individuals in the United States, a number that is anticipated to increase to approximately 14 million by 2050. In addition to cognitive decline, individuals diagnosed with AD typically experience behavioral and psychological symptoms including agitation and aggression. These symptoms are seen in a high percentage of AD sufferers with agitation being reported in up to 70% of patients. Agitation is characterized by emotional distress, aggressive behaviors, disruptive irritability, and disinhibition. Agitation associated with AD has been associated with increased caregiver burden, decreased functioning, earlier nursing home placement, and death.

Because there are no FDA-approved pharmacological treatments for the indication of agitation associated with AD, patients are currently treated off-label with various agents including antipsychotics, which have been considered the mainstay of treatment. These treatments however are limited by safety concerns. Typical antipsychotics prescribed for agitation, aggression, or insomnia are associated with functional decline in patients with AD, while studies indicate that atypical antipsychotics may be associated with increased rates of cerebrovascular events in patients with dementia.

Rationale for the Development of AXS-05 in Agitation associated with AD

The rationale for the use of AXS-05 for the treatment of agitation associated with AD is based on the mechanisms of action of DM, and preliminary clinical evidence of the effect of DM when co-administered with an inhibitor of its metabolism in agitation associated with AD.

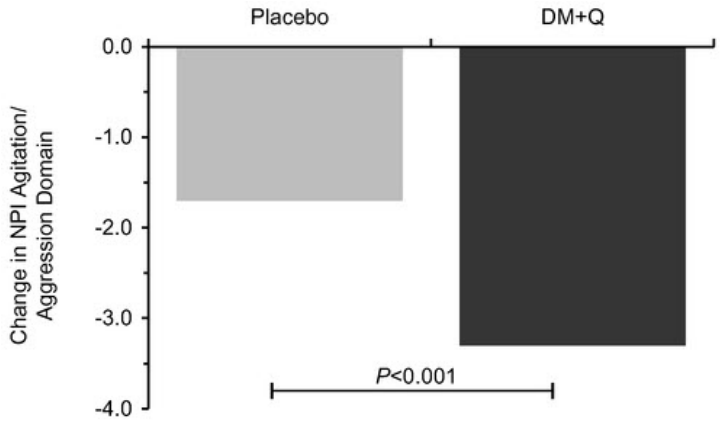
Mechanistic rationale. Mechanisms of action of DM include NMDA receptor antagonism and sigma-1 receptor agonism. Altered glutamate transmission via NMDA receptors has been suggested to play a role in behavioral changes in dementia, and clinical evidence suggests that NMDA antagonism may reduce agitation and aggression in AD patients. The pharmacologic action of agents used in the treatment of dementia, such as donepezil, and behavioral disorders, such as fluvoxamine, include sigma-1 receptor agonism.

Clinical Rationale. Administration of DM with an inhibitor of its metabolism has been shown to result in a statistically significant reduction in agitation associated with AD. The effects of DM co-administered with the metabolic inhibitor quinidine was studied in a third-party, randomized, double-blind, placebo-controlled, two-stage trial in 220 patients with probable AD and clinically meaningful agitation. In stage 1 of the study, patients were randomized to receive either placebo or DM with quinidine (20 mg DM / 10 mg quinidine once per day, titrated to 30 mg DM / 10 mg quinidine twice per day). In stage 2, patients initially on placebo were stratified according to response, then re-randomized to placebo or active treatment (titrated as in stage 1). Each stage lasted five weeks. The primary endpoint was the change in the agitation/aggression domain of the Neuropsychiatric Inventory, or NPI, assessed by combining results from the two stages.

The primary endpoint showed a statistically significant improvement with DM and quinidine as compared to placebo. During stage 1, a reduction of 3.3 in the agitation/aggression domain of the NPI was seen for active treatment as compared to a reduction of 1.7 for placebo, with a P value that is less than 0.001, as shown in the figure below. During stage 2, a reduction of 2.0 was observed for active treatment as compared to a reduction of 0.8 for placebo, with a P value that is equal to 0.02. Average baseline values for the agitation/aggression domain of the NPI were 7.1 for the active treatment group and 7.0 for the placebo group. Statistically significant improvements for the active treatment arm compared to placebo were also reported for the majority of secondary endpoints including the NPI total score, NPI-Caregiver Distress Score, Caregiver Strain Index, and Cornell Scale for Depression in Dementia. Moreover, treatment with DM and the metabolic inhibitor was not associated with cognitive decline as measured by the Mini Mental State Examination.

In the trial, patients were titrated to a 30 mg DM / 10 mg quinidine dose. According to the FDA package insert for Nuedexta, DM is the pharmacologically active ingredient of the DM / quinidine combination that acts on the CNS, with quinidine serving to increase DM plasma levels. The plasma concentrations of DM, measured using AUC_{0-12} and C_{max}, achieved with AXS-05 administration in our Phase 1 trials are in the range of those associated with a 30 mg DM / 10 mg quinidine dose, based on data in the FDA's public review documents for Nuedexta.

Change in Agitation/Aggression scores in AD with DM and metabolic inhibitor quinidine (Q) during stage 1



Source: *Am J Geriatr Psychiatry 2015; 23:3, Supplement 1, S164-S165.*

Smoking Cessation

We are developing AXS-05 as an aid to smoking cessation treatment. In December 2017, we entered into a collaboration with Duke University for the conduct of a Phase 2 trial of AXS-05 under an Investigator Sponsor IND in smokers interesting in quitting. Products that are currently approved in the United States as aids to smoking cessation treatment include Zyban, or bupropion, which is marketed by GlaxoSmithKline, Chantix, or varenicline, which is marketed by Pfizer Inc., and various types of nicotine replacement approaches.

Indication Overview

Nearly 40 million American adults smoke and around 70% report that they want to quit. Tobacco use results in approximately 500,000 premature deaths each year in the U.S., according to the Centers for Disease Control and Prevention. Smoking is the single largest cause of premature deaths worldwide accounting for an estimated 20% of all deaths in developed countries. Direct health care and lost productivity costs as a result of smoking total nearly $300 billion a year in the U.S. alone. It is estimated that only 3% to 5% of cigarette smokers who attempt to quit without assistance are successful for 6 to 12 months, and even with the currently available treatment options, relapse rates remain above 80%.

Rationale for the Development of AXS-05 in Smoking Cessation

The rationale for the use of AXS-05 as an aid to smoking cessation treatment is based on the mechanisms of action of DM and bupropion, nonclinical evidence of the effect of DM in models of nicotine dependence, and the established clinical efficacy of bupropion in the indication.

Results of preclinical studies conducted at Duke University demonstrated that the dextromethorphan component of AXS-05 significantly reduced nicotine self-administration in nicotine-dependent rats in a dose-dependent manner ($p<0.0005$ versus control). Results of pharmacokinetic clinical trials conducted by us have demonstrated that, in human subjects, AXS-05 results in a significant increase in dextromethorphan plasma concentrations ($p<0.0001$ versus administration of dextromethorphan as a single agent). Furthermore, bupropion, a component of AXS-05, has been found to be effective for smoking cessation in clinical trials. The preclinical and clinical efficacy of the individual components of AXS-05 combined with their positive pharmacokinetic interaction supports the potential for AXS-05 to be effective in the treatment of tobacco dependence in humans.

Clinical Development of AXS-05

We are developing AXS-05 and intend to seek FDA approval for the product utilizing the 505(b)(2) regulatory pathway. Section 505(b)(2) of the FDCA permits an applicant to file an NDA that relies, in part, on data not developed by or for the applicant and to which the applicant has not received a right of reference, such as the FDA's findings of safety and efficacy in the approval of a similar drug, or reference listed drug, or published literature, in support of its application. We have completed a Phase 2 trial of AXS-05 in MDD and three Phase 1 pharmacokinetic clinical trials of AXS-05.

We held a pre-IND meeting with the FDA in February 2015 where we discussed our clinical development plan for AXS-05 in TRD. Based on that meeting, we submitted an investigational new drug application, or IND, to the FDA to conduct two Phase 3 trials of AXS-05 in TRD to support an NDA filing for this indication.

In March 2016, we initiated the STRIDE-1 study, a Phase 3, randomized, double-blind, active-controlled trial to assess the efficacy and safety of AXS-05 in the treatment of TRD.

In January 2017, we received IND clearance from the FDA to proceed with our Phase 2/3 clinical trial of AXS-05 in agitation associated with AD.

In February 2017, we received Fast Track designation from the FDA for AXS-05 for TRD.

In July 2017, we initiated the ADVANCE-1 study, a Phase 2/3, randomized, double-blind, controlled trial to evaluate the efficacy and safety of AXS-05 in patients with agitation associated with AD.

In December 2017, we entered into a research collaboration agreement with Duke University to evaluate AXS-05 in a Phase 2 clinical trial in smoking cessation.

In April 2018, we announced the enrollment of the first patient into a Phase 2 clinical trial of AXS-05 for smoking cessation treatment, which is being conducted under a research collaboration agreement between us and Duke University.

In April 2018, we announced that an IDMC had conducted an interim futility analysis for the STRIDE-1 study. Based on the results of the analysis, the IDMC recommended that the trial continue. The IDMC also reviewed the available safety information from the study and indicated that, based on the interim results, AXS-05 appears safe and well-tolerated.

In June 2018, we initiated the ASCEND study, a Phase 2 randomized, double-blind, controlled trial to evaluate the efficacy and safety of AXS-05 in patients with MDD.

In December 2018, we announced that an IDMC had conducted an interim futility analysis for the ADVANCE-1 study. Based on the results of the analysis, the IDMC recommended continuation of the AXS-05 treatment arm. Additionally, the IDMC recommended no further randomization of subjects to the bupropion treatment arm of the study. The IDMC did not indicate that there were any safety concerns in the study.

In January 2019, we announced that AXS-05 met the prespecified primary endpoint and significantly improved symptoms of depression in the ASCEND study.

Completed ASCEND Study

We have completed the ASCEND Phase 2 study, a randomized, double-blind, active-controlled, multi-center, U.S. trial, in which 80 adult patients with confirmed moderate to severe MDD were treated either with AXS-05 (45 mg dextromethorphan/105 mg bupropion), or the active comparator bupropion (105 mg), twice daily for 6 weeks.

AXS-05 met the prespecified primary endpoint by demonstrating a highly statistically significant reduction in the Montgomery-Åsberg Depression Rating Scale, or MADRS, total score, averaged over the 6-week treatment period, the overall treatment effect, as compared to bupropion ($p<0.001$). At Week 6, AXS-05 demonstrated a 17.2 point reduction in the MADRS total score compared to a 12.1 point reduction for bupropion ($p=0.013$). AXS-05 rapidly reduced depressive symptoms, demonstrating a statistically significant improvement over bupropion on the Clinical Global Impression-Improvement scale (CGI-I) at Week 1 ($p=0.045$). Starting at Week 1, AXS-05 achieved numerical superiority over bupropion on the MADRS total score, with statistical significance achieved at Week 2 and maintained at all time points thereafter. At Week 6, 47% of patients who received AXS-05 achieved remission, prospectively defined as a score of 10 or less on the MADRS, compared with 16% of patients who received bupropion ($p=0.004$).

AXS-05 was superior to bupropion on multiple prespecified secondary endpoints, with statistically significant effects demonstrated on most, including the following: MADRS-6 ($p=0.007$ at Week 6); percentage of responders on MADRS-6, response defined as ≥ 50% reduction from baseline, ($p=0.014$ at Week 6); CGI-I ($p=0.045$ at Week 1, and 0.051 at Week 6); Clinical Global Impression-Severity scale, or CGI-S, ($p=0.038$ at Week 6); percentage of patients achieving remission on MADRS, remission defined as MADRS ≤ 10, ($p=0.004$ at Week 6). Additionally, the treatment effect observed with bupropion in the study was consistent with that observed in prior published trials.

Fifty-one percent of patients in the trial had experienced three or more major depressive episodes prior to enrollment. Twenty-three percent of study participants had received first line treatment in their current major depressive episode prior to treatment with study medication.

AXS-05 was safe and well tolerated with no serious adverse events. The most commonly reported adverse events in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite, and anxiety. Overall, rates of adverse events were similar between AXS-05 and bupropion. Retention of patients in the study was favorable overall and higher in the AXS-05 treatment arm. There was no meaningful difference between the two treatment arms in discontinuations due to adverse events. Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.

Completed Phase 1 Trials of AXS-05

We have completed three Phase 1 pharmacokinetic clinical trials of AXS-05. The objectives of these trials were to assess the pharmacokinetics of DM when co-administered with bupropion, and to assess the safety and tolerability of the combination. In the first two Phase 1 trials, the components of AXS-05, DM and bupropion, were co-administered as separate tablets. In the third Phase 1 trial, AXS-05 was dosed as a bilayer tablet. In each study, administration of bupropion in combination with DM resulted in substantial increases in DM plasma concentrations measured using C_{max} and AUC at all doses tested.

The first Phase 1 trial was a randomized, multiple-dose, open-label study to determine the pharmacokinetics of DM when various doses of DM are administered concomitantly with bupropion under fasting conditions, as well as the safety of the combination. Subjects were randomized to receive twice-daily administrations of 150 mg of bupropion in combination with DM at various doses up to 60 mg, or 60 mg of DM alone, for 8 consecutive days. Bupropion was titrated with subjects being dosed once daily for the first 3 days, then twice daily thereafter. A total of 32 healthy, adult volunteers were included in this study in four treatment groups. Full pharmacokinetic assessments were made on Day 1 and Day 8. For the dose of 60 mg of DM / 150 mg of bupropion, AUC_{0-12} and C_{max} values on Day 8 for DM when dosed in combination with bupropion were approximately 60 times and 40 times, respectively, the values for DM when dosed alone. For all doses tested, administration of DM in combination with bupropion resulted in substantial increases in AUC_{0-12} and C_{max} values of DM on Day 8 as compared to Day 1 of dosing. DM exposure measured using AUC and C_{max} increased in a dose dependent manner with increasing doses of DM. Administration of DM did not appear to affect the pharmacokinetics of bupropion.

There were no reported serious adverse events in the trial. The majority of treatment-emergent adverse events experienced were graded as mild or moderate in severity, and had resolved by the end of the study. The most commonly reported adverse events were dizziness, nausea, headache, insomnia, dry mouth, constipation, hypoesthesia, palpitation, disturbance in attention, tremor, and hyperhidrosis. Adverse events were reported more frequently in the AXS-05 arm as compared to the DM-only arm. The majority of these adverse events were expected with the administration of bupropion, having been already reported in the FDA package inserts for products containing bupropion.

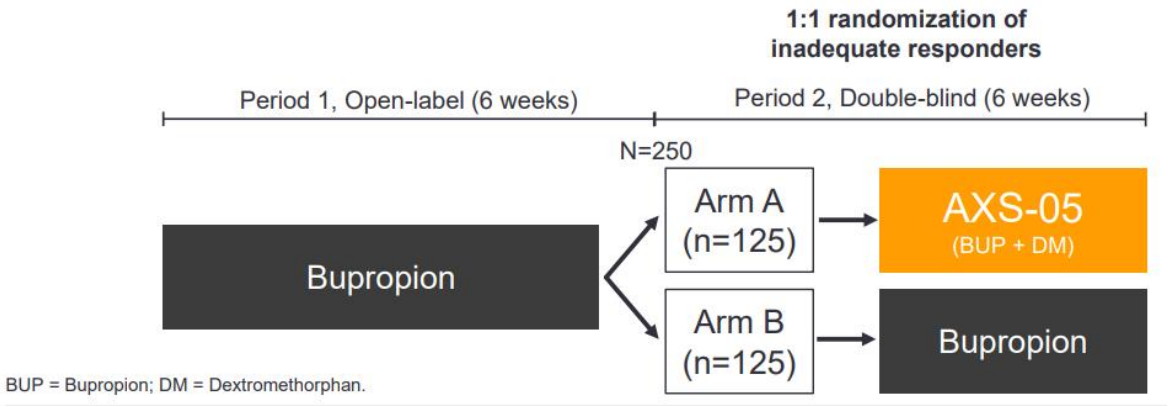
The second Phase 1 trial was a randomized, multiple-dose, open-label study to determine the pharmacokinetics of DM when various doses of DM are administered concomitantly with various doses of bupropion and to assess safety during co-administration of bupropion and DM. A total of 40 healthy, adult volunteers were included in this study in five treatment groups. Subjects were randomized to receive twice-daily administration of either 150 mg of bupropion alone, or combinations of varying doses of bupropion and DM for 8 consecutive days. Bupropion was titrated with subjects being dosed once daily for the first 3 days, then twice daily thereafter. Full pharmacokinetic assessments were made on Day 1 and Day 8. Similar to the results in our first study, administration of DM in combination with bupropion resulted in substantial increases in AUC_{0-12} and C_{max} values of DM on Day 8 as compared to Day 1 of dosing for all combinations tested. DM exposure measured using AUC and C_{max} increased in a dose-dependent manner as doses of either DM or bupropion were increased. Administration of DM did not appear to affect the pharmacokinetics of bupropion.

There were no reported serious adverse events in the trial. The majority of treatment-emergent adverse events experienced were graded as mild in severity, and had resolved by the end of the study. The most commonly reported adverse events were headache, nausea, dizziness, fatigue, increased heart rate, palpitations, constipation, diarrhea, increased blood pressure, and tremor. No particular trend was observed when comparing the rates or types of adverse events in the combination groups as compared to the group receiving bupropion alone.

The third Phase 1 trial was a randomized, multiple-dose, double-blind pharmacokinetic study of AXS-05 conducted using a single tablet containing DM and buproprion. In this study, which enrolled a total of 30 healthy, adult volunteers, administration of AXS-05 as a single tablet resulted in substantial increases in AUC_{0-12} and C_{max} values of DM compared to Day 1 levels similar to the increases observed in our first two Phase 1 studies. There were no reported serious adverse events in the trial. The majority of treatment-emergent adverse events experienced were graded as mild in severity, and had resolved by the end of the study. The most commonly reported adverse events were dizziness, fatigue, headache, and insomnia.

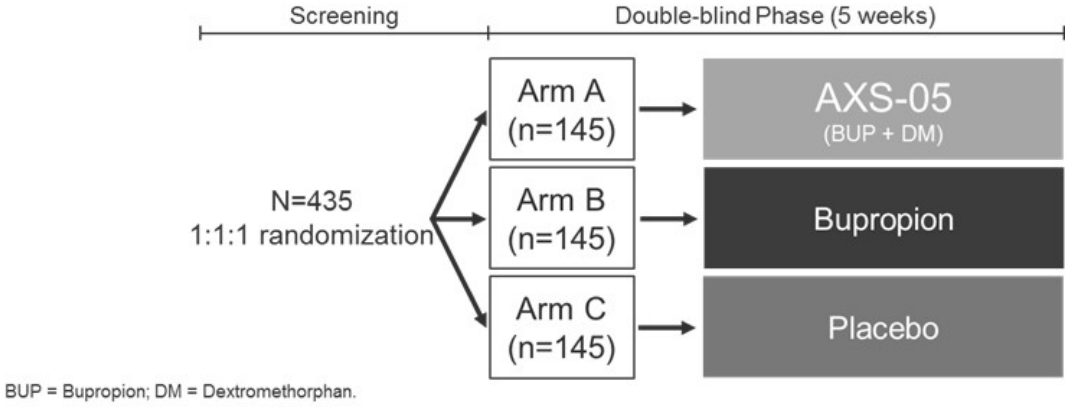
Ongoing STRIDE-1 Study

In March 2016, we initiated the STRIDE-1 study, a Phase 3, randomized, double-blind, active-controlled trial to assess the efficacy and safety of AXS-05 in the treatment of TRD. Patients with MDD who have had inadequate response to one or two antidepressant treatments are treated in an open-label fashion with bupropion during a 6-week lead-in period. Patients who had inadequate response to bupropion during this lead-in period are considered to have TRD and are randomly assigned in a 1:1 ratio to receive bupropion or AXS-05 under fasting conditions in a double-blind fashion for 6 weeks. The primary endpoint is the change in the MADRS after 6 weeks of treatment. In April 2018, an interim analysis was performed on the first approximately 40% of the target number of subjects to assess futility. The interim analysis was performed by an IDMC which recommended that the trial continue.



Ongoing ADVANCE-1 Study

In July 2017, we initiated the ADVANCE-1 study, a Phase 2/3, randomized, double-blind, controlled trial to evaluate the efficacy and safety of AXS-05 in patients with agitation associated with AD. Patients with probable AD and clinically significant agitation are randomly assigned in a 1:1:1 ratio to receive bupropion, placebo, or AXS-05 in a double-blind fashion. The primary endpoint is the change is the Cohen-Mansfield Agitation Inventory. The trial will randomize a total of approximately 435 patients. In December 2018, an interim analysis was performed on the first approximately 30% of the target number of subjects to assess futility. The interim analysis was conducted by an IDMC which recommended continuation of the AXS-05 arm and no further enrollment into the bupropion arm.



AXS-07

Overview

AXS-07 is novel, oral, investigational medicine consisting of MoSEIC™ meloxicam and rizatriptan. We are initially developing AXS-07 for the acute treatment of migraine. Meloxicam is a new molecular entity for migraine enabled by Axsome's MoSEIC technology, which results in rapid absorption of meloxicam while maintaining a long plasma half-life. Rizatriptan is FDA approved for the acute treatment of migraine as a single agent. The distinct mechanism of action and rapid absorption of MoSEIC™ meloxicam, combined with the known efficacy of rizatriptan, is designed to provide potentially rapid, superior and consistent relief of migraine pain, with lower symptom recurrence, as compared to currently available therapies.

Migraine

We are developing AXS-07 for the acute treatment of migraine. A majority of migraine sufferers indicate that they are not fully satisfied with currently available treatment options.

Indication Overview

Migraine is a disorder characterized by recurrent attacks of pulsating, unilateral or bilateral head pain, often associated with nausea, photobobia, and phonophobia. Migraine attacks may occur with or without an aura, which is a focal neurological symptom, such as vision changes, that typically precedes other symptoms. Migraine attacks generally last from 4 to 72 hours and are often severe and disabling, requiring bed rest.

Over 37 million Americans suffer from migraine according to the Centers for Disease Control, and it is the leading cause of disability among neurological disorders in the United States according to the American Migraine Foundation. It is estimated that migraine accounts for $78 billion in direct costs, such as doctor visits and medications, and indirect costs, such as missed work and lost productivity, each year in the United States. Published surveys of migraine sufferers indicate that more than 70% are not fully satisfied with their current treatment, that nearly 80% would try a new therapy, and that they desire treatments that work faster, more consistently, and result in less symptom recurrence.

Rationale for the Development of AXS-07 in Migraine

The rationale for the development of AXS-07 in the treatment of migraine is based on the potentially rapid absorption and long half-life of MoSEIC™ meloxicam, and the additive and potentially synergistic efficacy resulting from the distinct mechanisms of action of meloxicam and rizatriptan. The meloxicam component of AXS-07 is a COX-2 preferential NSAID that inhibits the synthesis of prostaglandins, may reduce meningeal inflammation and inhibit central sensitization resulting from the activation of glial cells in the brain stem. Meloxicam is a new molecular entity for migraine and is not currently approved for this indication. Axsome's MoSEIC™ technology enables meloxicam's use in this indication by potentially significantly increasing the speed of its absorption after oral administration. The rizatriptan component of AXS-07 is a 5-$HT_{1B/D}$ agonist that inhibits CGRP–mediated vasodilation, has been shown to have central trigeminal antinociceptive activity, and may reduce the release of inflammatory mediators from trigeminal nerves. Rizatriptan is currently approved as a single agent for the acute treatment of migraine.

By combining rizatriptan with MoSEIC™ meloxicam, AXS-07 may overcome some the limitations of current acute treatments which include incomplete pain relief, suboptimal onset of action, and recurrence of symptoms. MoSEIC™ meloxicam contributes a distinct mechanism of action, and potentially reaches therapeutic plasma conentrations rapidly after oral administration, thereby providing the potential for greater efficacy and a more rapid onset of action as compared to current treatments. In addition, MoSEIC™ meloxicam potentially maintains an approximately 20-hour half-life, which may provide more sustained efficacy with less recurrence of symptoms as compared to current treatments. Less recurrence would be expected to result in reduced use of rescue or repeat medication.

Based on AXS-07's multiple mechanisms of action, the unique pharmacokinetics of the MoSEIC™ meloxicam component, and results from numerous clinical trials with the rizatriptan component, we believe that AXS-07 may have advantages over currently available therapy in the acute treatment of migraine:

- *Rapid absorption and onset of action.* In a completed Phase 1 trial of tablets consisting of MoSEIC™ meloxicam and esomeprazole, therapeutic plasma levels of meloxicam were attained within 15 minutes of oral dosing of MoSEIC™ meloxicam, with a median time to maximum plasma concentration (T_{max}) that was 9 times faster for MoSEIC™ meloxicam as compared to standard meloxicam (0.5 hour versus 4.5 hours for MoSEIC™ and standard meloxicam, respectively, $p<0.0001$). The potentially fast absorption of MoSEIC™ meloxicam in AXS-07 combined with a reported T_{max} for rizatriptan of 1 to 1.5 hours would be expected to result in rapid onset of migraine pain relief with AXS-07.

- *Strong and consistent pain relief.* AXS-07 has the potential to provide efficacy that is superior to currently available migraine treatments based on the expected additive effect of MoSEIC™ meloxicam and rizatriptan.

- *Sustained pain relief.* The approximately 20-hour half-life of MoSEIC™ meloxicam, observed with tablets consisting of MoSEIC™ meloxicam and esomeprazole, combined with the expected additive effect of the rizatriptan component of AXS-07 may result in a more sustained effect with less recurrence of symptoms with AXS-07 as compared to currently available treatments.

- *Pharmacoeconomic benefits.* The potentially superior efficacy of AXS-07 would be expected to result in reduced use of medical services, rescue or repeat medication, absenteeism, and loss of productivity, as compared to currently available treatments.

Clinical Development of AXS-07

We are developing AXS-07 and intend to seek FDA approval for the product utilizing the 505(b)(2) regulatory pathway.

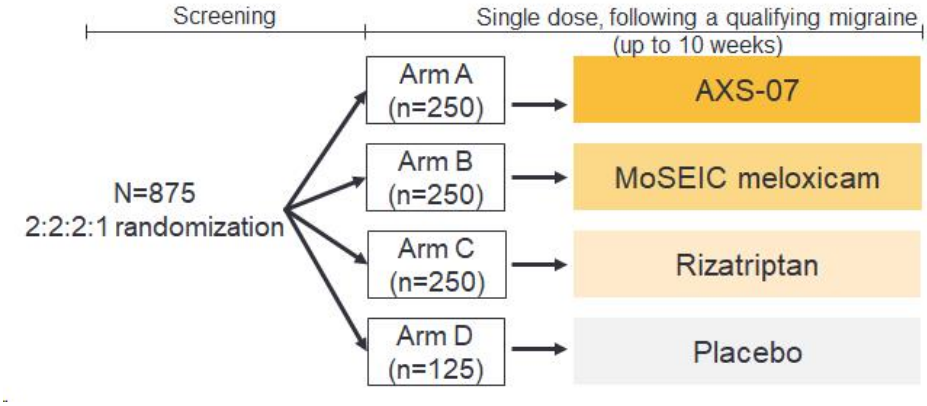
We received written pre-IND meeting guidance from the FDA in August 2017 on our clinical development plan for AXS-07 in migraine.

In February 2019, we reached agreement with the FDA under an SPA for the design, endpoints, and statistical approach of the planned MOMENTUM (Maximizing Outcomes in Treating Acute Migraine) Phase 3 trial of AXS-07 in the acute treatment of migraine. Based on FDA feedback during this SPA process, Axsome believes that only one Phase 3 trial may be needed for the approval of AXS-07.

In March 2019, we initiated the MOMENTUM study.

Ongoing MOMENTUM Study

In March 2019, we initiated the MOMENTUM study, a Phase 3, randomized, double-blind, multicenter, controlled trial to assess the efficacy and safety of AXS-07 in the acute treatment of migraine. Approximately 875 patients, with a history of inadequate response to prior migraine treatments, will be randomized in a 2:2:2:1 ratio to treatment with AXS-07, rizatriptan, meloxicam, or placebo. The two co-primary endpoints of the trial are the proportion of patients who are free from headache pain two hours after dosing, and the proportion of patients who no longer suffer from their most bothersome migraine-associated symptom (nausea, photophobia, phonophobia) two hours after dosing.



AXS-09

AXS-09 is a novel, oral, investigational medicine consisting of chirally pure esbupropion and DM. Esbupropion is the *S*-enantiomer of bupropion, a dopamine and norepinephrine reuptake inhibitor and nicotinic acetylcholine receptor antagonist which also serves to increase the bioavailability of DM. Enantiomers are molecules which are identical in chemical structure but which differ in the three-dimensional arrangement of the atoms, i.e. the molecules are mirror images. AXS-09 may potentially be applicable to the treatment of a variety of CNS disorders, based on the mechanisms of action of its two components.

In February 2018, we announced the results of a Phase 1 pharmacokinetic trial of AXS-09. The Phase 1 trial was a randomized, multiple-dose, parallel group pharmacokinetic trial. A total of 32 healthy adult subjects were randomly assigned to treatment with AXS-09, *R*-bupropion and DM, single-entity *S*-bupropion, or single-entity *R*-bupropion tablets, for 8 days under fasting conditions. Plasma concentrations of DM, bupropion, and their metabolites were measured. The primary endpoint was the change in DM plasma concentrations from day 1 to day 8.

Results of the Phase 1 trial demonstrated that AXS-09 resulted in substantial increases in DM plasma concentrations into a potentially therapeutic range with repeated dosing, $p<0.0001$ day 1 versus day 8. AXS-09 was well tolerated with no serious adverse events reported in the trial. The increased plasma concentrations of DM after dosing with AXS-09, which contains the chirally pure *S*-enantiomer of bupropion, are comparable to those achieved with dosing of our first generation product candidate, AXS-05, which contains racemic bupropion, equal amounts of the *S*- and *R*-enantiomers. Results of this Phase 1 trial coupled with preclinical data also indicate the potential for enhanced absorption and therapeutic effect of the *S*-enantiomer as compared to the *R*-enantiomer.

AXS-12

Overview

AXS-12, reboxetine, is a novel, oral, investigational medicine that we are initially developing for the treatment of the symptoms of narcolepsy. AXS-12 is a highly selective and potent norepinephrine reuptake inhibitor.

Narcolepsy

Indication Overview

Narcolepsy is a serious and debilitating neurological condition that causes dysregulation of the sleep-wake cycle and is characterized clinically by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis, and disrupted nocturnal sleep. Narcolepsy afflicts an estimated 185,000 individuals in the U.S. Cataplexy is seen in an estimated 70% of narcolepsy patients and is a sudden reduction or loss of muscle tone while a patient is awake, typically triggered by strong emotions such as laughter, fear, anger, stress, or excitement. Narcolepsy interferes with cognitive, psychological, and social functioning, increases the risk of work- and driving-related accidents, and is associated with a 1.5 fold higher mortality rate. Depression is reported in up to 57% of patients.

Rationale for the Development of AXS-12 in Narcolepsy

That rationale for the development of AXS-12 in narcolepsy is supported by positive pre-clinical and preliminary clinical results in narcolepsy, and an extensive clinical safety record. Reboxetine, the active agent in AXS-12, significantly and dose-dependently reduced narcoleptic episodes in hypocretin (orexin)-deficient mice, a well-established genetic animal model of narcolepsy. In an open-label pilot trial, reboxetine treatment improved excessive daytime sleepiness and reduced cataplexy in patients with narcolepsy. Reboxetine has an extensive safety record in Europe and in over 40 countries where it is approved for the treatment of depression. Depression is reported in up to 57% of narcolepsy patients.

Clinical Development of AXS-12

We received written pre-IND meeting guidance from the FDA in August 2018 on our clinical development plan for AXS-12 in narcolepsy.

In October 2018, we received Orphan Drug Designation from the FDA for AXS-12 for the treatment of narcolepsy.

In January 2019, we initiated the CONCERT study, a Phase 2 randomized, double-blind, controlled trial to evaluate the efficacy and safety of AXS-12 in narcolepsy.

Ongoing CONCERT Study

In January 2019, we initiated the CONCERT study, a Phase 2, double-blind, randomized, placebo-controlled, crossover, multicenter trial to assess the efficacy and safety of AXS-12 in patients with narcolepsy. The study will enroll approximately 20 patients, all of whom will be treated with AXS-12 for three weeks, and with placebo for three weeks. Eligible patients will be randomized to receive either AXS-12 followed by placebo, or placebo followed by AXS-12. Efficacy assessments will include the frequency of cataplexy attacks, and measures of other symptoms of narcolepsy.

Axsome PPC Product Candidates

The assets in Axsome PPC include three Phase 3-stage product candidates. Two of the product candidates, AXS-02 and AXS-06, are being developed directly by Axsome, and one of the candidates, neridronic acid, or neridronate, is covered by Axsome's intellectual property portfolio. These product candidates are being developed for five different indications including the signs and symptoms of osteoarthritis and rheumatoid arthritis, osteoporosis, the pain of knee osteoarthritis, chronic low back pain, and complex regional pain syndrome.

AXS-02

Overview

AXS-02 is a novel, targeted investigational pain therapeutic. It is an orally administered, non-opioid agent with a new mechanism of action for the treatment of pain. We are developing AXS-02 for the treatment of the pain of knee OA associated with BMLs, and for the treatment of CLBP associated with MCs. No drug is currently approved by the FDA or the EMA specifically for these targeted subsets of knee OA and CLBP. AXS-02 is also being developed for the treatment of osteoporosis.

We believe that, if successfully developed, AXS-02 may overcome many of the limitations of current treatments for pain, and may be attractive to patients and their physicians, based on the following differentiating features:

- Novel osteoclast-inhibiting mechanism of action for the treatment of pain
- Targeted therapy approach that utilizes radiographic biomarkers to identify appropriate patients
- Oral administration
- Convenient weekly dosing and short course of treatment
- Potential for extended duration of pain relief
- Lack of opioid-related side effects and abuse and addiction potential

We initiated a Phase 3 trial with AXS-02 for the treatment of pain in patients with knee OA associated with BMLs in March 2016. We have received IND clearance from the FDA to proceed with our planned Phase 3 clinical trial of AXS-02 in CLBP and plan to initiate the Phase 3 clinical trial upon the availability of resources.

Novel Mechanisms of Action for Pain

Zoledronic acid, the active molecule in AXS-02, is a potent nitrogen-containing bisphosphonate. Bisphosphonates are compounds that bind with high affinity to bone mineral and inhibit the bone-resorbing cells called osteoclasts. Zoledronic acid reduces osteoclast activity by inhibiting a critical enzyme called farnesyl pyrophosphate synthase, or FPPS. Zoledronic acid is the bisphosphonate with the strongest affinity for bone and the highest inhibitory activity of FPPS. Osteoclasts resorb bone by secreting protons and generating an acidic extracellular microenvironment. The secreted protons may directly excite pain receptors, which are found in mineralized bone. We believe that zoledronic acid may therefore reduce pain by inhibiting osteoclast hyperactivity and suppressing the up-regulation of acid-sensing ion channels on sensory neurons. Zoledronic acid has also been shown to inhibit the production of pro-inflammatory cytokines and to have anti-angiogenic properties.

Targeted Therapy for Pain

We are developing AXS-02 for specific subsets of patients who display certain target lesions or specific pathology that we believe may be addressed by the mechanisms of action of our product candidate. The target lesions include BMLs, and MCs. We are including only patients with BMLs in our registration trial of AXS-02 for the pain of knee OA, and plan to only include patients with MCs in our registration trials of AXS-02 for CLBP. These target lesions exhibit increased bone turnover, which is potentially inhibited by zoledronic acid. Furthermore, because zoledronic acid localizes preferentially to sites of high bone turnover, we believe it may specifically target these sites of disease activity in knee OA and CLBP. We believe that this targeted approach may result in a less heterogeneous patient population in our clinical trials, improve our ability to demonstrate a treatment effect, and, if approved, enable treatment of more appropriate patient populations.

Orally Administered

AXS-02 is a novel oral formulation of zoledronic acid. Zoledronic acid is currently marketed only as an intravenous, or IV, preparation and is not currently approved for the treatment of pain. Our oral formulation uses a disodium salt of zoledronic acid, which exhibits substantially improved solubility as compared to the diacid form. This improved solubility may facilitate oral absorption.

Oral administration is non-invasive, less costly, more convenient, and less burdensome to patients and prescribers as compared to IV dosing. Oral administration provides greater prescribing flexibility for clinicians and convenience for patients since it allows them to self-administer the therapy at home and avoid having to travel to and from a hospital or infusion facility. Additionally, based on clinical experience with currently approved bisphosphonates, oral administration of zoledronic acid may have certain safety advantages as compared to IV dosing.

In a recent trial of 6,097 patients treated over 3 years who received either IV zoledronic acid therapy or oral therapy with alternative bisphosphonates, 76% and 73% of patients indicated a preference for oral versus IV formulations if all agents showed equal efficacy at randomization and therapy completion, respectively.

Infrequent Dosing and Convenient Regimen

The potency and pharmacokinetics of zoledronic acid may allow for very infrequent dosing and for a short and convenient treatment regimen. Because of its convenient administration and limited treatment duration, we believe that AXS-02, if successfully developed, may improve compliance and be preferred by patients and their physicians over currently available treatments.

Extended Pain Relief

AXS-02 may provide pain relief of long duration based on results of trials conducted with IV-administered zoledronic acid. In trials in patients with knee OA and BMLs and CLBP associated with MCs, treatment with IV-administered zoledronic acid resulted in pain relief that was measurable one or more months after cessation of treatment. For example, pain reduction as compared to placebo was demonstrated 6 months after treatment in knee OA, and 1 month after treatment in CLBP. Furthermore, 1 year after treatment, a statistically significant reduction was observed in the percentage of zoledronic acid-treated patients with CLBP who were taking non-steroidal anti-inflammatory drugs, or NSAIDs, as compared to placebo-treated patients. This observed extended pain reduction may be related to the potency of zoledronic acid and its long residence time in bone.

Lack of Opioid-related Side Effects and Abuse and Addiction Potential

Reflecting the currently limited treatment options for chronic pain, opioid medications are widely prescribed despite their numerous significant undesirable side effects and potential consequences. These side effects and consequences include dependency, addiction and abuse potential, respiratory depression, hypotension, constipation, and a higher incidence of falls and fractures in older patients. Prescription opioids are also increasingly associated with deaths from unintentional overdose, with over 16,000 deaths reported in the United States each year.

AXS-02 exerts its potential effects for the treatment of pain via novel non-opioid mechanisms of action. If successfully developed, AXS-02 would represent an alternative treatment for pain that lacks the addiction and abuse potential and other serious side effects of opioids.

Knee Osteoarthritis (OA) Associated with Bone Marrow Lesions (BMLs)

We are developing AXS-02 for the treatment of the pain of knee OA associated with BMLs. There is currently no therapy specifically approved by the FDA or the EMA to treat this subset of knee OA. The FDA has agreed to an SPA for our ongoing Phase 3 COAST-1 study in subjects with knee OA and BMLs. The FDA has also granted Fast Track designation for AXS-02 for the treatment of the pain of knee OA associated with BMLs.

Indication Overview

Knee OA is a disorder characterized by periarticular bone changes, progressive loss of articular cartilage, joint space narrowing, and eventual total joint failure. It is clinically manifested by knee pain, significant physical disability, and reduced quality of life. While currently available drug therapies attempt to address the pain of knee OA, they are not thought to address the cause of the pain.

Recently, BMLs have been recognized as an important feature of knee OA because of their relation to the pain and pathogenesis of the condition. BMLs appear as areas of increased signal intensity on MRI of the knee, and represent regions of increased subchondral bone turnover. BMLs are clinically relevant because they are associated with and predict knee pain, disease severity, and structural progression in patients with knee OA, based on published studies. Findings from several cross-sectional and longitudinal studies have demonstrated that (1) BMLs are strongly associated with the presence and severity of pain in patients with knee OA, (2) new or enlarging BMLs are associated with increased pain and diminishing BMLs with decreased pain, (3) BMLs are associated with progression of joint space narrowing and cartilage loss, (4) BMLs predict knee joint replacement, and (5) increasing BML size is associated with cartilage loss. These studies therefore suggest that BMLs are a source of knee pain and a potential target for pharmaceutical intervention.

There is currently no therapy specifically approved by the FDA or the EMA to treat the pain of knee OA associated with BMLs. Currently available therapy for the broader knee OA population include non-pharmacological treatments, oral and topical medications, and intra-articular injections. Non-pharmacological approaches include exercise, weight management, strength training, self-management, and education. Oral treatments include acetaminophen, selective and non-selective NSAIDs, and opioid medications. Intra-articular injections for knee OA include intra-articular hyaluronic acid, or IAHA, and intra-articular corticosteroids, or IACS. These treatments are generally short-acting and may address the symptoms of knee OA, but are not thought to have an effect on the underlying cause of the condition. Knee joint replacement surgery is viewed as a last resort for patients who, despite pharmacological and non-pharmacological treatment, do not have adequate pain relief and functional improvement.

Results of epidemiological studies suggest that there are approximately 25 million patients in the United States, 50 years of age and older, with radiographic knee OA. Approximately 12 million of these patients are estimated to be symptomatic, 7 million of whom we estimate have BMLs.

Rationale for the Use of AXS-02 in the Pain of Knee OA Associated with BMLs

The rationale for utilizing AXS-02 for the treatment of the pain of knee OA associated with BMLs is based on the observations that (1) BMLs are strongly associated with pain in knee OA, (2) BMLs represent regions of increased subchondral bone turnover and reduced mineral content based on studies of BMLs resected from human subjects, and (3) zoledronic acid potently inhibits bone turnover, increases bone mineral density, and localizes preferentially to regions of increased bone turnover. The pharmacological actions of zoledronic acid therefore suggest the potential for AXS-02 to affect BMLs, thereby reducing pain in patients with knee OA associated with BMLs.

Chronic Low Back Pain (CLBP) Associated with Modic Changes (MCs)

We are developing AXS-02 for the treatment of CLBP associated with MCs. There is currently no therapy specifically approved by the FDA or the EMA to treat this subset of CLBP.

Indication Overview

CLBP is defined as persistent or fluctuating low back pain lasting at least three months. It is a disabling and costly condition that is associated with increased healthcare utilization. The economic costs of CLBP are estimated to range from $12.2 billion to $90.6 billion annually in the United States. Factors that contribute to this economic impact include prolonged loss of function, consequent loss of work productivity, treatment costs, and disability payments. Low back pain may be due to a specific cause such as fracture, tumor, infection, or nerve root compression. However, it is estimated that in more than 85% of cases such specific causes cannot be identified, resulting in the majority of cases being classified as non-specific.

Recently, it has been suggested that patients with MCs may represent a specific clinical subgroup of CLBP patients. MCs are vertebral bone marrow changes that are visible on MRI of the spine, and that represent regions of increased bone turnover and pro-inflammatory mediators. MCs are classified into types 1, 2, or 3, based on radiographic and histological features. MCs are clinically relevant because they are associated with low back pain, based on published studies. Findings from studies in clinical and non-clinical populations have demonstrated that the presence of MCs, especially type 1 MCs, is correlated with low back pain, predicts persistent symptoms, and sick leaves, and is associated with poor outcomes. These studies therefore suggest that MCs are a potential target for pharmaceutical intervention.

There is currently no therapy specifically approved by the FDA or the EMA to treat CLBP associated with MCs. Currently available therapy for the broader CLBP population includes non-pharmacological approaches, such as exercise, and pharmacological treatments, such as NSAIDs and opioid medications. Current pharmacological treatments are generally short-acting and may address the symptoms of CLBP, but are not thought to have an effect on the underlying cause of the condition.

Results of epidemiological studies suggest that there are approximately 121 million adults in the United States with low back pain in a given year. Approximately 9 million of these sufferers are estimated to have CLBP, of whom we estimate approximately 1.6 million have type 1 MCs.

Rationale for the Use of AXS-02 in CLBP Associated with MCs

The rationale for utilizing AXS-02 for the treatment of CLBP associated with MCs is based on the observations that (1) MCs are associated with low back pain, (2) MCs represent regions of increased bone turnover based on three-phase bone scans and increased pro-inflammatory cytokines and vascular density based on analysis of lesions resected from human subjects, and (3) zoledronic acid potently inhibits bone turnover, may reduce pro-inflammatory cytokine production, is anti-angiogenic, and localizes preferentially to regions of increased turnover. The pharmacological actions of zoledronic acid therefore suggest the potential for AXS-02 to affect MCs, thereby reducing pain in patients with CLBP associated with MCs.

Clinical Development of AXS-02

We are developing AXS-02 and intend to seek FDA approval for the product candidate utilizing the 505(b)(2) regulatory pathway. We currently plan to rely on the FDA's prior finding of safety and efficacy for IV-administered zoledronic acid as well as published literature to support our marketing application.

We held a Type C meeting with the FDA in June 2014 where we presented our clinical development plan for AXS-02 in the treatment of pain associated with CRPS, the pain of knee OA associated with BMLs, and CLBP associated with MCs.

In October 2015, we reached agreement with the FDA regarding an SPA on the design of a Phase 3 clinical trial with AXS-02 for the treatment of the pain of knee OA associated with BMLs. An SPA documents the FDA's agreement that the design and planned analysis of a clinical trial adequately address scientific and regulatory objectives that, if met, would support a regulatory submission for approval of a drug. An SPA, however, does not guarantee FDA approval.

In April 2016, we received Fast Track designation from the FDA for AXS-02 for the treatment of the pain of knee OA associated with BMLs. The FDA's Fast Track designation program is designed to aid in the development and expedite the review of drugs that are intended to treat serious or life-threatening conditions. In order to receive Fast Track designation, a product candidate must also demonstrate the potential to address an unmet medical need. Fast Track designation provides greater access to, and more frequent communication with, the FDA throughout the entire drug development and review process, with the goal of getting important new drugs to patients more rapidly. It also provides the opportunity to submit sections of an NDA on a rolling basis, where the FDA may review portions of the NDA as they are received instead of waiting for the entire NDA submission. In addition, Fast Track designated product candidates may be eligible for priority review at the time of NDA submission.

In February 2017, we received IND clearance from the FDA to proceed with our planned Phase 3 clinical trial of AXS-02 in CLBP.

As discussed below, we had previously initiated a Phase 3 clinical trial of AXS-02 for the treatment of complex regional pain syndrome, or CRPS, which we referred to as the CREATE-1 trial. In January 2018, an independent data monitoring committee, or IDMC, conducted an interim analysis of the CREATE-1 trial of AXS-02 in CRPS and of the COAST-1 trial of AXS-02 in knee OA associated with BMLs. The IDMC recommended that the COAST-1 trial be continued to full enrollment, and that the CREATE-1 trial be stopped for futility.

We completed oral toxicology studies in the rat and dog models to support the dosing of AXS-02 in our completed Phase 1 trial and in our ongoing and planned Phase 3 trials. Dose-limiting adverse effects were primarily gastrointestinal related. We have completed a Phase 1 trial of AXS-02 to characterize the pharmacokinetics of zoledronic acid and its effects on markers of bone resorption after oral administration of AXS-02. In this trial, oral administration of AXS-02 tablets resulted in rapid absorption of zoledronic acid and marked suppression of bone resorption markers.

The potential effect of zoledronic acid on the pain of knee OA associated with BMLs has been demonstrated in a Phase 2, investigator-initiated, randomized, double-blind, placebo-controlled trial. In this trial, IV administration of zoledronic acid resulted in a statistically significant reduction in pain and BML size at 6 months. The potential effect of zoledronic acid in CLBP associated with MCs has been demonstrated in a Phase 2, investigator-initiated, randomized, double-blind, placebo-controlled trial. In this trial, IV administration of zoledronic acid resulted in statistically significant reductions in pain at 1 month and NSAID use at 12 months. We have obtained exclusive rights to the data generated from this trial in CLBP.

We are currently conducting a randomized, double-blind, placebo-controlled Phase 3 trial of AXS-02 in patients with knee OA associated with BMLs. In February 2017, we received IND clearance from the FDA to proceed with our planned Phase 3 clinical trial of AXS-02 in CLBP. We believe our planned Phase 3 dosing of AXS-02 will provide cumulative systemic exposure of zoledronic acid that is similar to that achieved with the 5 mg IV dose used in the Phase 2 trials in knee OA and CLBP, based on the results of our completed Phase 1 trial.

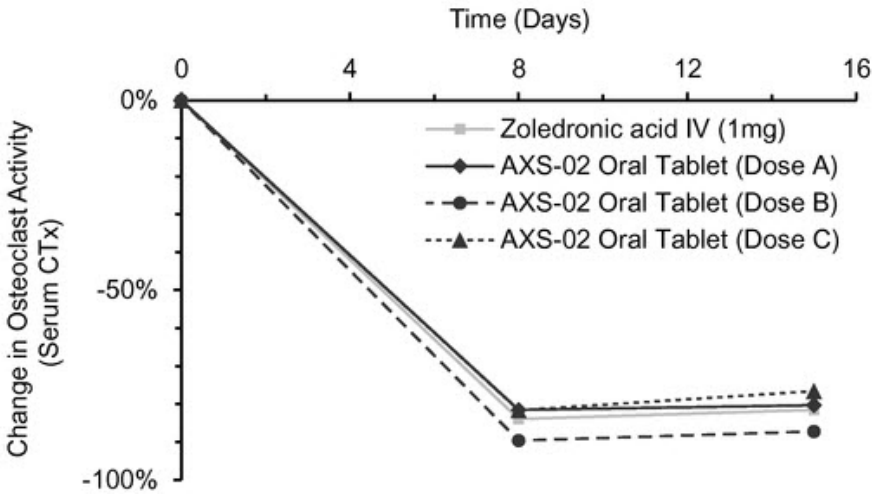
Completed Phase 1 Trial of AXS-02

We conducted a Phase 1 trial to assess the fasting pharmacokinetics, pharmacodynamics, safety, and tolerability of orally administered AXS-02 tablets in healthy adult male and postmenopausal female volunteers under a Health Canada Clinical Trial Application. The trial was a randomized, open-label, partial crossover study in a total of 36 subjects. Each subject received two of the following four treatments: three varying oral doses of AXS-02 or a 1 mg IV dose of zoledronic acid. Each treatment was separated by a wash-out period of at least 14 days. Blood samples were collected prior to dosing and after dosing to measure zoledronic acid plasma concentrations and the effect of AXS-02 on biomarkers of bone resorption, including serum CTx.

Zoledronic acid was rapidly absorbed after oral administration of AXS-02 tablets with median time to reach the maximum plasma concentration, or T_{max}, of 30 to 45 minutes. The absolute oral bioavailability of zoledronic acid after administration of AXS-02 tablets found in this trial was greater than that reported for oral bisphosphonate agents currently marketed in the United States, based on FDA package inserts. Zoledronic acid plasma concentrations after oral administration of AXS-02, measured using area under the plasma concentration curve, or AUC, and maximum plasma concentration, or C_{max}, were found to be dose proportional in the range tested using the power model.

Oral administration of AXS-02 resulted in marked reductions of biomarkers of bone resorption. For example, as shown in the figure below, levels of serum CTx were reduced by approximately 80 to 90% seven days after dosing. This effect was generally maintained 14 to 15 days after dosing.

Serum CTx change from baseline after oral administration of varying doses of AXS-02, and IV administration of 1 mg zoledronic acid



There were no reported serious adverse events in the trial. The majority of treatment-emergent adverse events experienced were graded as mild or moderate in severity, were transient in nature, and were completely resolved by the end of the study. The most commonly reported adverse events were headache, fever, musculoskeletal pain, diarrhea, abdominal pain, nausea, myalgia, and chills. Adverse events were reported more frequently with increasing oral doses, and more frequently in the oral dose groups than in the IV dose group.

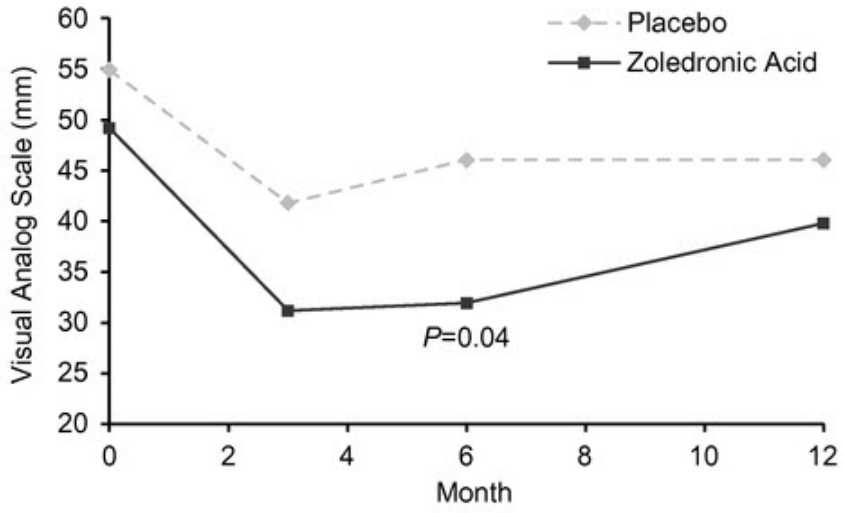
Phase 2 of Zoledronic Acid in the Pain of Knee OA Associated with BMLs

IV-administered zoledronic acid, the active molecule in AXS-02, was tested in an investigator-initiated, single-center, randomized, double-blind, placebo-controlled trial in patients with knee OA and BMLs. In this trial, zoledronic acid treatment reduced pain and BML size, as further described below, demonstrating an effect on symptom and structure. The design and results of this trial have been reported in a peer-reviewed journal.

In the trial, 59 patients, aged 50 to 80 years, with clinical knee OA and knee BMLs on MRI were randomized in a 1:1 ratio to receive either a single 5-mg IV infusion of zoledronic acid or placebo. BMLs were determined using proton density-weighted fat saturation magnetic resonance images at baseline, 6, and 12 months. Pain intensity was measured at baseline, 3, 6, and 12 months using a 100-mm visual analogue scale, or VAS, which is a standard clinical measurement for pain severity. Total BML area was measured in square millimeters at baseline, 6, and 12 months. The primary outcomes were the change from baseline to 6 months in pain intensity as measured by the VAS, and maximal area of BML measured at 6 months. Participants were allowed to remain on their background pain medications but the dose was kept constant through the trial period where possible. One subject randomized to placebo received zoledronic acid. Therefore, data for this patient was included in the zoledronic acid arm in the analyses and results discussed below. This analysis is referred to as a per protocol analysis.

At baseline, the mean VAS score was 54 mm. As shown in the figure below, there was a statistically significant reduction in pain intensity, measured using the VAS, from baseline to 6 months in the zoledronic acid-treated group as compared to placebo, using the per protocol analysis. Changes in pain intensity between baseline and the other time points were numerically greater in the zoledronic acid arm than in the placebo arm but were not statistically significant.

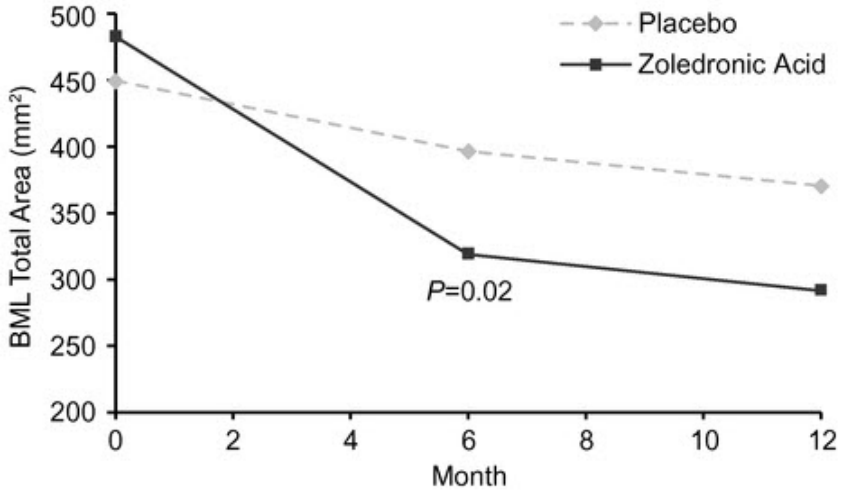
Pain intensity over time in knee OA patients with BMLs treated with zoledronic acid or placebo



Source: Derived from *Laslett et al. Ann Rheum Dis. 2012;71:1322-1328.*

As shown in the figure below, there was a statistically significant reduction in BML area at 6 months in the zoledronic acid-treated group as compared to placebo. At the 12 month assessment, the changes in BML size were lower in magnitude in the zoledronic acid arm as compared to the placebo arm and were not statistically significant.

BML area over time in subjects treated with zoledronic acid or placebo



Source: Derived from *Laslett et al. Ann Rheum Dis. 2012;71:1322-1328.*

The most commonly reported adverse events were acute phase reactions, which are primarily cold or flu-like symptoms and headaches. Adverse events occurred more frequently in the zoledronic acid-treated group. Serious adverse events were primarily non-elective hospital admissions, none of which were considered causally related to study drug.

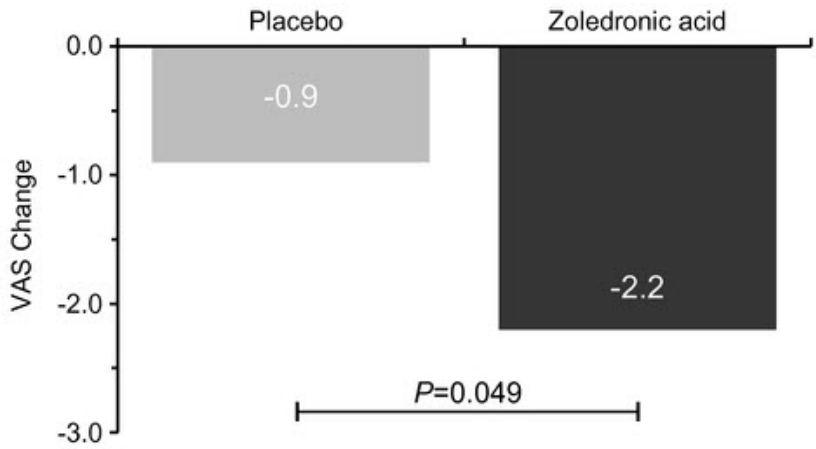
Phase 2 of Zoledronic Acid in CLBP Associated with MCs

IV-administered zoledronic acid was tested in an investigator-initiated, single-center, randomized, double-blind, placebo-controlled trial in patients with CLBP associated with MCs. In this trial, zoledronic acid treatment resulted in statistically significant reductions in pain at 1 month and NSAID use at 12 months. We have exclusive rights to reference these trial data.

In the trial, 40 patients, with a mean age of approximately 50 years, with low back pain lasting at least 3 months and MCs on MRI, were randomized in a 1:1 ratio to receive either a single 5-mg IV infusion of zoledronic acid or placebo. MCs were determined on MRI performed within 6 months prior to enrollment. Other inclusion criteria included pain intensity of at least 6 cm on a 10-cm VAS or an Oswestry Disability Index, or ODI, of at least 30%. Low back pain intensity was measured at screening and 1 and 12 months after infusion using a 10-cm VAS. The primary outcome was the change in low back pain intensity as measured by the VAS. Pain medication use was inquired about during study visits.

Study participants had a mean low back pain duration of 293 days at study entry, and initial low back pain intensity of 6.7 on the VAS. All patients displayed either type 1, type 2, or mixed type 1 and type 2 MCs on MRI. As shown in the figure below, there was a statistically significant reduction in pain intensity, measured using the VAS, at 1 month in the zoledronic acid-treated group as compared to placebo. Changes in pain intensity at 12 months were numerically greater in the zoledronic acid arm than in the placebo arm but were not statistically significant.

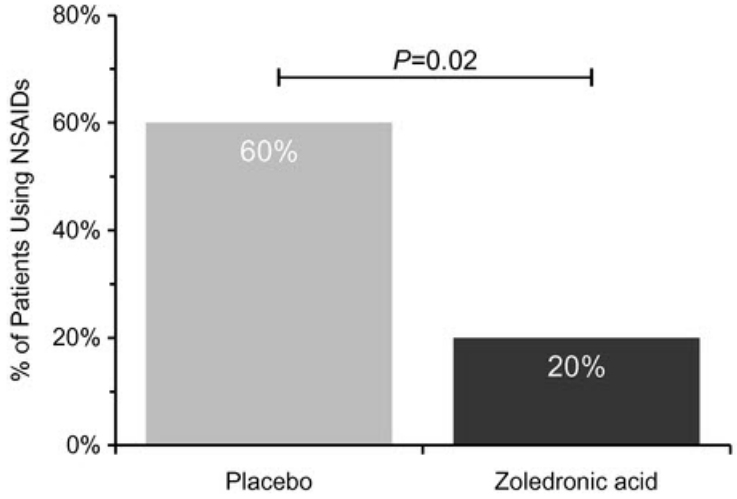
Change in pain intensity at 1 month in CLBP patients treated with zoledronic acid or placebo



As shown in the figure below, at 1 year only 20% of patients in the zoledronic acid treatment group reported using NSAIDs compared to 60% of patients in the placebo group. At baseline, there were no differences in self-reported use of NSAIDs between the treatment groups.

The most commonly reported adverse events were acute phase reactions, which occurred more frequently in the zoledronic acid-treated group. The majority of the acute phase reactions were rated mild to moderate in severity and typically resolved within three days of onset. Sinusitis requiring temporary hospitalization following zoledronic acid infusion was reported in one patient and was therefore classified as a serious adverse event.

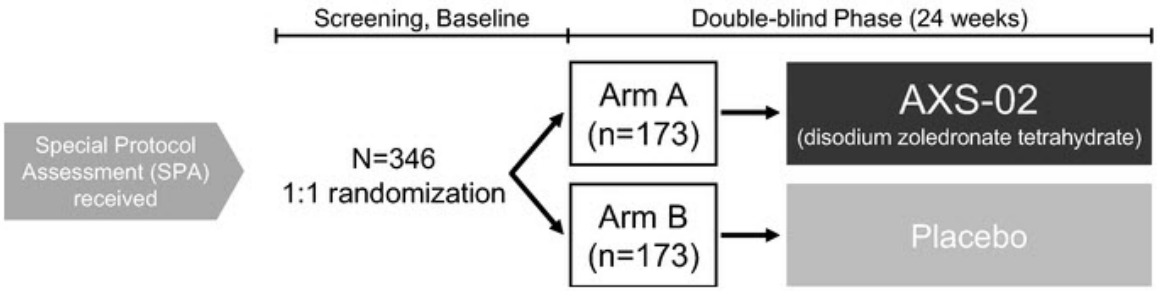
NSAID use at 1 year in CLBP patients treated with zoledronic acid or placebo



Ongoing COAST-1 Study

In March 2016, we initiated the COAST-1 study, a Phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of AXS-02 in the treatment of the pain of knee OA associated with BMLs. This trial will enroll approximately 346 patients with clinically diagnosed knee OA and at least one confirmed BML in the affected knee on MRI. Eligible patients must be at least 50 years of age, either male or postmenopausal female, and have at least moderate pain intensity. The COAST-1 study is being conducted pursuant to an FDA SPA.

After a baseline period, patients meeting the entry criteria are randomized in a 1:1 ratio to receive either (1) AXS-02 tablets once per week or (2) matching placebo tablets once per week, under fasting conditions for 6 weeks. Randomized patients remain blinded for an additional 18 weeks, totaling 24 weeks for the double-blind phase. The primary endpoint is the change in pain intensity from baseline to week 24, measured using the NRS. A pre-planned interim analysis was performed by an IDMC on the first 77 subjects enrolled in the trial. The IDMC recommended that the COAST-1 trial be continued to full enrollment. The IDMC also reviewed the available safety information in the study and confirmed that AXS-02 was safe and generally well-tolerated. Screening of subjects in this trial was paused pending results of the interim analysis, and will resume after readouts from our ongoing Phase 3 trial in TRD.



Planned Phase 3 Trial in CLBP Associated with MCs

We intend to initiate a Phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of AXS-02 in the treatment of CLBP associated with MCs. This trial is anticipated to enroll patients with low back pain lasting at least 3 months and confirmed type 1 or mixed type 1 and type 2 MCs on MRI. After a baseline period, patients meeting the entry criteria will be randomized in a 1:1 ratio to receive either (1) AXS-02 tablets once per week or (2) matching placebo tablets once per week, under fasting conditions for 6 weeks. Randomized patients will remain blinded for an additional 6 weeks, totaling 12 weeks for the double-blind phase. The primary endpoint is anticipated to be the change in pain intensity from baseline to week 12, measured using the NRS. We anticipate that the trial will enroll a total of approximately 300 patients. We received IND clearance from the FDA to proceed with our planned Phase 3 clinical trial of AXS-02 in CLBP. The initiation of this clinical trial is contingent upon the availability of resources.

CREATE-1 Study

In July 2015, we initiated the CREATE-1 study, a Phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of AXS-02 in the treatment of pain associated with complex regional pain syndrome, or CRPS. An interim analysis was conducted to assess the efficacy and safety of AXS-02 and included 81 subjects. The IDMC recommended that the CREATE-1 trial be stopped for futility. The IDMC also reviewed the available safety information in the study and confirmed that AXS-02 was safe and generally well-tolerated. Additionally, AXS-02 treatment resulted in a significant reduction of serum CTx, a marker of bone resorption, as compared to placebo ($p<0.0001$). Pursuant to the IDMC recommendation, we have discontinued enrollment in this study and are conducting study close-out activities.

Osteoporosis

Osteoporosis is a degenerative bone condition characterized by an imbalance in bone resorption and formation resulting in porous and brittle bones that are prone to fracture. Increased bone turnover markers, especially serum CTx, are associated with a higher incidence of osteoporosis and fracture risk. An estimated 200 million women are affected worldwide by osteoporosis, resulting in over 8.9 million fractures annually. Osteoporotic fractures occur in 1 in 3 women over age 50 and in 1 in 5 men over age 50. In 2017, worldwide sales of branded osteoporosis drugs totaled over $7.3 billion.

The potential for AXS-02 in the treatment of osteoporosis is currently being evaluated in a Phase 2 trial examining the ability of orally administered AXS-02 to reduce bone resorption over a 12-month period following a single 6-week treatment course consisting of one tablet a week for 6 weeks. Zoledronic acid, the active ingredient in AXS-02, is currently approved for the treatment of osteoporosis but is currently available only as an intravenous formulation. In contrast, AXS-02 is a novel oral formulation that has resulted in rapid absorption of zoledronic acid. The ongoing Phase 2 trial enrolled patients with complex regional pain syndrome who had been treated in the CREATE-1 trial. As previously reported, in that study, AXS-02 treatment resulted in a significant reduction of serum CTx, considered the reference standard marker of bone resorption by the International Osteoporosis Foundation, as compared to placebo, $p<0.0001$, three months after a single treatment course. The current Phase 2 trial is examining the durability of this effect up to one year after treatment.

Neridronic Acid

Neridronic acid, or neridronate, is a Phase 3-stage, intravenously administered bisphosphonate compound whose use for the treatment of certain pain conditions, including CRPS, is covered by more than 20 issued Axsome patents which provide protection out to 2033. CRPS is a debilitating condition characterized by severe, continuous, burning or throbbing pain in a limb. It is considered to be one of the most painful conditions, results in loss of physical function, and can lead to significant and sometimes permanent disability. Axsome’s extensive CRPS intellectual property portfolio reflects Axsome’s early and continued efforts and commitment to develop an effective treatment for this debilitating condition for which there is currently no approved drug.

Neridronic acid is currently being studied in two pivotal Phase 3 trials for the treatment of CRPS by Grünenthal GmbH, or Grünenthal. The Phase 3 trials were announced in June 2018 and are investigating the efficacy and safety of neridronic acid in 360 patients with CRPS. Grünenthal has filed post grant reviews, or PGRs, on five of the issued patents covering neridronic acid for the treatment of CRPS. Neridronic acid has been granted Breakthrough Therapy, Fast Track, and Orphan Drug designations for the treatment of CRPS by the FDA. The Breakthrough Therapy designation is supported by data from a randomized, double-blind, placebo-controlled Phase 2 clinical trial showing significant reduction in pain and symptoms of CRPS with neridronic acid treatment, according to public disclosures.

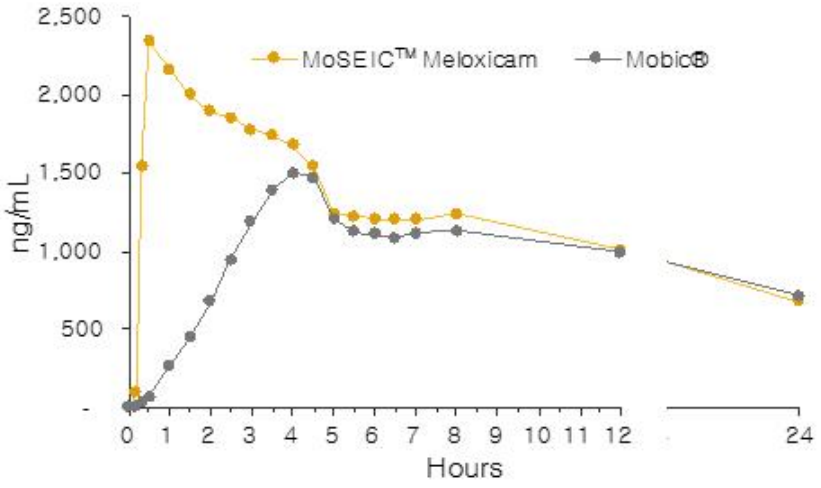
MoSEIC™ Technology

Overview

The MoSEIC™, or Molecular Solubility Enhanced Inclusion Complex, technology was developed to improve the absorption of drug molecules after oral administration. Using a proprietary process, target drug molecules are combined with solubility enhancers to form inclusion complexes, which are then stabilized using a buffering system, to improve drug release and enhance absorption. We are currently developing two clinical-stage product candidates, AXS-07 and AXS-06, that utilize the MoSEIC technology to substantially increase the solubility and speed the absorption of meloxicam while maintaining durability of action.

We have completed a Phase 1 pharmacokinetic clinical trial of MoSEIC™ meloxicam, in combination with esomeprazole, under a clinical trial application with Health Canada.

Scientific Rationale



Meloxicam is a potent and well characterized nonsteroidal anti-inflammatory drug, or NSAID, whose utility in acute pain has been limited by slow absorption resulting in a delayed T_{max}. Our MoSEIC meloxicam technology is designed to improve the solubility of meloxicam thereby enhancing its absorption resulting in a reduced T_{max} as compared to standard meloxicam. As shown in the figure above, results of our completed Phase 1 trial of MoSEIC meloxicam revealed a rapid T_{max} after oral administration, of 0.5 hour versus 4.5 hours for standard meloxicam.

AXS-06

Overview

AXS-06 is a novel, oral, investigational medicine consisting of MoSEIC™ meloxicam and esomeprazole. We are initially developing AXS-06 for the treatment of osteoarthritis and rheumatoid arthritis. Esomeprazole is a proton pump inhibitor, or PPI, which lowers stomach acidity and which has been shown to reduce the occurrence of NSAID-induced gastrointestinal ulcers. AXS-06 is designed to provide rapid, effective pain relief, and to reduce the risk of NSAID-induced ulcers, with convenient once-daily dosing.

Osteoarthritis and Rheumathoid Arthritis

We are developing AXS-06 for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis, and reduction in the risk of developing upper gastrointestinal ulcers in patients at risk of developing NSAID-associated upper gastrointestinal ulcers.

Indication Overview

Rheumatoid arthritis, or RA, is a chronic, systemic, inflammatory disease that affects connective tissue and is characterized by joint pain and destruction. RA is the most common type of autoimmune arthritis. Although joints, primarily in the hands and feet, are the primary target of RA, extra-articular manifestations can have a significant impact on other organ systems. According to the American College of Rheumatology, more than 1.3 million Americans suffer from RA.

Osteoarthritis, or OA, is a degenerative joint disease, which mainly affects the articular cartilage. It is associated with ageing and most often affects the knees, hips, fingers, and lower spine region. OA is the most common form of arthritis. According to the Centers for Disease Control and Prevention, more than 30 million American adults suffer from OA.

Rationale for the Development of AXS-06 in OA and RA

Meloxicam is a well-characterized NSAID that is approved for the treatment of the signs and symptoms of OA and RA, and is marketed under the tradename Mobic®. Meloxicam is a long-acting NSAID with COX-2 preferential inhibition. Its long half-life allows for once-daily dosing. However standard meloxicam has an extended time to maximum plasma concentration or T_{max} which may result in a slow onset of analgesic action. In addition, like other NSAIDs, meloxicam can induce upper gastrointestinal ulcers which can be complicated by the development of bleeding, perforation or obstruction. Chronic use of NSAIDs has been reported to be associated with the development of gastrointestinal ulcers in as many as 25% of patients. AXS-06 is designed to overcome these limitations by combining a rapidly absorbed formulation of meloxicam with esomeprazole, an agent that has been proven to reduce the incidence of NSAID-associated gastrointestinal ulcers.

Esomeprazole is a well-known PPI that is approved for the treatment of gastroesophageal reflux disease, and for the reduction of NSAID-associated gastric ulcers. It is marketed under the tradename Nexium® as a single agent. Esomeprazole is also approved as part of a fixed-dose combination with naproxen, under the tradename Vimovo®, for the reduction of NSAID-associated gastric ulcers. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity.

Clinical Development of AXS-06

We are developing AXS-06 and intend to seek FDA approval for the product utilizing the 505(b)(2) regulatory pathway. We have completed one Phase 1 pharmacokinetic clinical trial of AXS-06 under a clinical trial application with Health Canada.

We received written pre-IND meeting guidance from the FDA in July 2017 on our clinical development plan for AXS-06 in OA and RA. Based on that meeting, we intend to submit an IND to the FDA and we believe that AXS-06 is Phase 3-ready.

Completed Phase 1 Trial

We conducted a Phase 1 trial to assess the fasting pharmacokinetics, pharmacodynamics, safety, and tolerability of orally administered MoSEIC meloxicam in combination with esomeprazole, our AXS-06 product candidate. Esomeprazole is a proton pump inhibitor which lowers stomach acidity and which has been shown to reduce the occurrence of NSAID-induced gastrointestinal ulcers. The trial was a randomized, parallel group trial to evaluate the pharmacokinetics and safety of meloxicam and esomeprazole after single and multiple dose administration of AXS-06 in healthy volunteers. A total of 30 subjects were randomly assigned in a 1:1:1 ratio to treatment with AXS-06 tablets (15 mg meloxicam, 40 mg esomeprazole), Mobic® tablets (15 mg meloxicam), or Nexium® capsules (40 mg esomeprazole), once daily for 6 days under fasting conditions. The primary endpoint was the T_{max} of meloxicam. Secondary endpoints included C_{max}, time to half maximum concentration, and time to therapeutic concentration.

The median T_{max} for meloxicam, the trial's primary endpoint, was 9 times faster for AXS-06 as compared to Mobic®, 0.5 hour versus 4.5 hours for AXS-06 and Mobic, respectively, $p<0.0001$. AXS-06 also demonstrated higher mean C_{max}, $p=0.0018$, faster time to therapeutic plasma concentration, $p<0.0001$, and time to half-maximal plasma concentration, $p<0.0001$, as compared to Mobic®. Terminal half-lives for meloxicam were similar for AXS-06 and Mobic® at approximately 20 and 22 hours, respectively. Plasma concentrations and terminal half-lives of esomeprazole after AXS-06 and Nexium® administration were comparable. AXS-06 was well tolerated with reported adverse events being similar across the three treatment arms. There were no serious adverse events in the study.

Commercial Agreements

We have customary clinical supply agreements and customary agreements with clinical research organizations to help manage our clinical trials. Each of our commercial agreements are non-exclusive, and we have no material contractual obligations under such agreements, except to the extent we order supply or request services to be performed.

Material License Agreements

In 2012, we entered into three exclusive license agreements with Antecip Bioventures II LLC, or Antecip, an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which we were granted exclusive licenses to develop, manufacture, and commercialize Antecip's patents and applications related to the development of AXS-05 and AXS-02, as well as AXS-04, a product candidate that is currently in early stage development, anywhere in the world for veterinary and human therapeutic and diagnostic use. The agreements were amended in August 2015 to update the schedule of patents and applications subject to the license agreements. Pursuant to the agreements, we are required to use commercially reasonable efforts to develop, obtain regulatory approval for, and commercialize AXS-05, AXS-02, and AXS-04. Under the terms of the agreements, we are required to pay to Antecip a royalty equal to 4.5% for AXS-02, 3.0% for AXS-05, and 1.5% for AXS-04, of net sales of products containing the licensed technology by us, our affiliates, or permitted sublicensees. These royalty payments are subject to reduction by an amount up to 50.0% of any required payments to third parties. Unless earlier terminated by a party for cause or by us for convenience, the agreements remain in effect on a product-by-product and country-by-country basis until the later to occur of (1) the applicable product is no longer covered by a valid claim in that country or (2) 10 years from the first commercial sale of the applicable product in that country. Upon expiration of the agreements with respect to a product in a country, our license grant for that product in that country will become a fully paid-up, royalty-free, perpetual non-exclusive license. If Antecip terminates any of the agreements for cause, or if we exercise our right to terminate any of the agreements for convenience, the rights granted to us under such terminated agreement will revert to Antecip. To date, we have not been required to make any payments to Antecip under any of the license agreements.

Intellectual Property

We seek to protect our product candidates and our technology through a combination of patents, trade secrets, proprietary know-how, FDA and EMA exclusivity, and contractual restrictions on disclosure. Our policy is to pursue, maintain, and defend patent rights whether developed internally or licensed from third parties and to protect the proprietary position of our product candidates by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions, and improvements that are important to the development of our business. U.S. patents generally have a term of 20 years from the earliest effective date of the application.

As of March 11, 2019, our intellectual property portfolio contains 192 issued patents and more than 165 pending applications in the United States and worldwide. Thirty-one issued United States patents and three issued foreign patents covering our AXS-05 product candidate have claims covering pharmaceutical composition, drug delivery, and pharmacokinetics with protection extending through 2034 for our issued and pending applications. Ninety-nine issued United States patents and 51 issued foreign patents covering our AXS-02 product candidate, and related compounds, have claims covering various aspects, including method of delivery, pharmacokinetics, composition of matter, and methods of use with protection extending through 2034 for both our issued patents and pending applications. Six issued United States patents and two issued foreign patents covering our AXS-07 and AXS-06 product candidates, and related compounds, have claims covering various aspects, including pharmacokinetics, pharmaceutical composition, method of delivery and methods of use with protection extending through 2036 for both our issued patents and pending applications. We have pending PCT applications, as well as pending applications in Australia, Canada, China, Europe, Hong Kong, Israel, Japan, Malaysia, Mexico, Singapore, South Korea, and New Zealand. We have other patent applications with claims covering the other programs in our pipeline, including those that are not relevant to our current programs in development. We have licensed the patents and pending applications which cover AXS-02, AXS-04, and AXS-05 from Antecip. All of the other components of our intellectual property portfolio are owned by us.

Many pharmaceutical companies, biotechnology companies, and academic institutions are competing with us in the field of pain and CNS disorders and filing patent applications potentially relevant to our business. In order to contend with the inevitable possibility of third-party intellectual property conflicts, from time to time we review and assess the third-party intellectual property landscape for competitive and other developments that may inform or impact our intellectual property development and commercialization strategies. With respect to third-party intellectual property, it is impossible to establish with certainty that our product candidates or discovery platform will be free of claims by third-party intellectual property holders or whether we will require licenses from such third parties. Even with modern databases and on-line search engines, literature searches are imperfect and may fail to identify relevant patents and published applications. Even when a third-party patent is identified, we may conclude, upon a thorough analysis, that we do not infringe the patent or that the patent is invalid. If the third-party patent owner disagrees with our conclusion and we continue with the business activity in question, we might have patent litigation forced upon us. Alternatively, we might decide to initiate litigation in an attempt to have a court declare the third-party patent invalid or not infringed by our activity. In either scenario, patent litigation typically is costly and time consuming, and the outcome is uncertain. The outcome of patent litigation is subject to uncertainties that cannot be quantified in advance, for example, the credibility of expert witnesses who may disagree on technical interpretation of scientific data. Ultimately, in the case of an adverse outcome in litigation, we could be prevented from commercializing a product or using certain aspects of our discovery platform as a result of patent infringement claims asserted against us. This could have a material adverse effect on our business. In addition to patents, we rely upon unpatented trade secrets, know-how, and continuing technological innovation to develop and maintain a competitive position. We seek to protect our proprietary information, including our trade secrets and proprietary know-how, by requiring our employees to execute Proprietary Information, Inventions, Non-Solicitation, and Non-Competition Agreements upon the commencement of their employment. Consultants and other advisors are required to sign consulting agreements. These agreements generally provide that all confidential information developed or made known during the course of the relationship with us be kept confidential and not be disclosed to third parties except in specific circumstances. In the case of our employees, the agreements also typically provide that all inventions resulting from work performed for us, utilizing our property, or relating to our business and conceived or completed during employment shall be our exclusive property to the extent permitted by law. Further, we require confidentiality agreements from entities that receive our confidential data or materials.

Sales and Marketing

We intend to build a commercial infrastructure in the United States in advance of anticipated drug approval of our product candidates. We believe that we can cost-effectively implement a targeted sales force required to commercialize our products, if approved, in the United States for the treatment of the pain of knee OA associated with BMLs, and CLBP associated with MCs. Support for this team will include sales management, internal sales support, distribution support, and an internal marketing group. Additional requisite capabilities will include focused management of key accounts such as managed care organizations, group purchasing organizations, and government accounts. We may seek co-promotion partners for our sales efforts to reach other United States physician groups, such as primary care physicians. We believe that there are significant market opportunities for our products outside of the United States. As a result, we plan to seek strategic partnerships with third parties, which may have greater reach and resources by virtue of their size and experience in the field, for the development and commercialization of our products outside the United States. We may elect in the future to utilize strategic partners, distributors, or contract sales forces to assist in the commercialization of our products. In order to implement this infrastructure, we will have to allocate management resources and make significant financial investments including some prior to product approval.

Scientific Advisors

In March 2015, we formed a Depression Scientific Advisory Board, or SAB, composed of leading experts in the areas of depression, FDA regulations, and clinical trial design. These experts provide key scientific, clinical, and strategic guidance concerning our development programs in depression and other CNS disorders. The following members were appointed to our Depression SAB: Maurizio Fava, M.D., Director of the Clinical Research Program and Executive Vice Chair of the Department of Psychiatry at Massachusetts General Hospital, and Slater Family Professor of Psychiatry at Harvard Medical School; Thomas Laughren, M.D., retired Division Director of the FDA's Division of Psychiatry Products; and Dan Iosifescu, M.D., Associate Professor, Department of Psychiatry at NYU Langone Medical Center, and Consultant in Psychiatry at Massachusetts General Hospital. We also benefit from the guidance of our other scientific advisors in the areas of AD, smoking cessation, migraine, knee OA, CLBP, and clinical trial design.

Competition

Overview

Our industry is highly competitive and subject to rapid and significant technological change. The large size and expanding scope of the pain and CNS markets make them attractive therapeutic areas for biopharmaceutical businesses. Our potential competitors include pharmaceutical, biotechnology, and specialty pharmaceutical companies. While we believe that our employees and consultants, scientific knowledge, technology, and development experience provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical, and biotechnology companies, academic institutions and governmental agencies, and public and private research institutions. Several of these entities have robust drug pipelines, readily available capital, and established research and development organizations. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Small or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the level of branded and generic competition, and the availability of reimbursement from government and other third-party payors.

CNS Product Candidates

AXS-05 Competition

Patients with MDD are typically treated with a variety of anti-depressant medications such as SSRIs and SNRIs. Some of these treatments include: Prozac, which is marketed by Eli Lilly and Company; Zoloft, which is marketed by Pfizer, Inc.; Effexor, which is marketed by Pfizer, Inc. and Wellbutrin, which is marketed by GlaxoSmithKline. There are two medications approved for the treatment of TRD, Symbyax, which is marketed by Eli Lilly and Company, and Spravato, which is marketed by Janssen Pharmaceuticals, Inc. We are aware of several companies developing compounds for the treatment of depression including Sage Therapeutics, Inc. and VistaGen Therapeutics, Inc. We are aware of other companies working to develop therapeutics for the treatment of agitation associated with AD, including Otsuka Pharmaceutical Co. Ltd., which is working to develop a combination of DM and quinidine for this indication. Products approved for smoking cessation include Chantix, which is marketed by Pfizer, Inc.; Zyban, which is marketed by GlaxoSmithKline; and various nicotine replacement therapies including skin patches, chewing gums, and lozenges.

AXS-07 Competition

There are a number of products approved for the acute treatment of migraine including Maxalt, which is marketed by Merck & Co., Inc.; and Treximet, which is marketed by Pernix Therapeutics Holdings, Inc. We are aware of several companies developing compounds for the treatment of migraine including Alder BioPharmaceuticals, Inc.; Allergan plc; Amgen Inc.; Biohaven Pharmaceutical Holding Company Ltd.; and Eli Lilly and Company.

AXS-12 Competition

Products approved to treat the symptoms of narcolepsy include Ritalin, which is marketed by Novartis Pharmaceuticals; Provigil and Nuvigil, which are both marketed by Teva Pharmaceutical Industries Ltd; and Xyrem, which is marketed by Jazz Pharmaceuticals plc. We are aware of several companies developing compounds for the treatment of the symptoms of narcolepsy including Avadel Pharmaceuticals plc; Harmony Biosciences LLC; and Jazz Pharmaceuticals plc.

Axsome PPC Product Candidates

AXS-02 Competition

Companies working to develop therapeutics for the treatment of pain associated with knee OA include Flexion Therapeutics, Inc.; Regeneron Pharmaceuticals Inc.; and Levolta Pharmaceuticals, Inc., which is developing an IV zoledronic acid product for the treatment of knee OA. We are aware of one company attempting to develop oral dosage forms of zoledronic acid for the treatment of complex regional pain syndrome, Grunenthal GmbH.

AXS-06 Competition

Patients with osteoarthritis and rheumatoid arthritis are typically treated with over-the-counter NSAIDs, prescription NSAIDs, corticosteroids, opioids, biologic agents and topical analgesics. Companies working to develop therapeutics for the treatment of pain associated with osteoarthritis and rheumatoid arthritis include Eli Lilly and Company; Flexion Therapeutics, Inc; GlaxoSmithKline; Pfizer, Inc.; Regeneron Pharmaceuticals Inc.; and Teva Pharmaceuticals Industries Ltd.

Neridronic Acid Competition

We are aware of one company working to develop neridronate for the treatment of certain pain conditions, including CRPS: Grünenthal GmbH.

Manufacturing

Manufacturing of drugs and product candidates are done by third-parties and manufacturing of both drug substance and drug product must comply with FDA current good manufacturing practice, or cGMP, regulations. Our product candidates comprise synthetic small molecules made through a series of organic chemistry steps starting with commercially available organic chemical raw materials. We do not currently own or operate any manufacturing facilities for the clinical or commercial production of our drug candidates. We conduct manufacturing activities under individual purchase orders with independent contract manufacturing organizations, or CMOs, to supply our clinical trials. We conduct periodic quality audits of their facilities. We believe that our existing suppliers of our product candidate active pharmaceutical ingredients and finished products will be capable of providing sufficient quantities of each to meet our clinical trial supply needs. Other CMOs may be used in the future for clinical supplies and, subject to approval, commercial manufacturing.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state, and local level, and in other countries and supranational regions, extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import, and export of pharmaceutical products such as those we are developing. In addition, healthcare regulatory bodies in the United States and around the world impose a range of requirements related to the payment for pharmaceutical products, including laws intended to prevent fraud, waste, and abuse of healthcare dollars. This includes for example, requirements that manufacturers of pharmaceutical products participating in Medicaid and Medicare comply with mandatory price reporting, discount, rebate requirements, and other cost control measures, as well as anti-kickback laws and laws prohibiting false claims. Some states also have enacted fraud, waste, and abuse laws that parallel (and in some cases apply more broadly than) federal laws, and in some cases price transparency requirements. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources. Further, healthcare is an active area of governmental scrutiny, and it is reasonable to expect that the requirements may become more stringent within the foreseeable future.

FDA Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process required by the FDA before product candidates may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies, and formulation studies in compliance with the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an IND which must become effective before human clinical trials may begin;
- approval by an independent Institutional Review Board, or IRB, for each clinical site or centrally, before each trial may be initiated;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug candidates for its intended use, performed in accordance with current Good Clinical Practices, or GCP;
- development of manufacturing processes in compliance with current Good Manufacturing Practices (cGMPs) to ensure the drug's identity, strength, quality, and purity;
- compilation of required information and submission to the FDA of an NDA;

- satisfactory completion of an FDA advisory committee review, if applicable;

- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMPs, and to assure that the facilities, methods, and controls are adequate to preserve the drug's identity, strength, quality, and purity, as well as satisfactory completion of an FDA inspection of selected clinical sites and selected clinical investigators to determine GCP compliance; and

- FDA review and approval of the NDA to permit commercial marketing for particular indications for use.

Preclinical Studies and IND Submission

The testing and approval process of product candidates requires substantial time, effort, and financial resources. Preclinical studies include laboratory evaluation of drug substance chemistry, pharmacology, toxicity, and drug product formulation, as well as animal studies to assess potential safety and efficacy. Such studies must generally be conducted in accordance with the FDA's Good Laboratory Practice regulations. Prior to commencing the first clinical trial with a product candidate, an IND sponsor must submit the results of the preclinical tests and preclinical literature, together with manufacturing information, analytical data, any available clinical data or literature, and proposed clinical study protocols, among other things, to the FDA as part of an IND. In the case of 505(b)(2) applications, though, some of the IND components may not be required (for example, if previously established for an approved drug which is referenced). Some preclinical testing may continue even after the IND is submitted.

An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, notifies the applicant of safety concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Clinical holds also may be imposed by the FDA at any time before or during trials due to safety concerns or noncompliance. As a result, submission of an IND may not result in FDA authorization to commence a clinical trial.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirements that all research subjects provide their informed consent in writing for their participation in any clinical trial, as well as review and approval of the study by an IRB. Investigators must also provide certain information to the clinical trial sponsors to allow the sponsors to make certain financial disclosures to the FDA. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the trial procedures, the parameters to be used in monitoring safety, the effectiveness criteria to be evaluated, and a statistical analysis plan. A protocol for each clinical trial, and any subsequent protocol amendments, must be submitted to the FDA as part of the IND. In addition, an IRB at each study site participating in the clinical trial or a central IRB must review and approve the plan for any clinical trial, informed consent forms, and communications to study subjects before a study commences at that site. An IRB considers, among other things, whether the risks to individuals participating in the trials are minimized and are reasonable in relation to anticipated benefits and whether the planned human subject protections are adequate. The IRB must continue to oversee the clinical trial while it is being conducted. Once an IND is in effect, each new clinical protocol and any amendments to the protocol must be submitted to the IND for FDA review, and to the IRB for approval. Progress reports detailing the results of the clinical trials must also be submitted at least annually to the FDA and the IRB and more frequently if serious adverse events or other significant safety information is found.

Information about certain clinical trials, including a description of the study and study results, must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their clinicaltrials.gov website.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group regularly reviews accumulated data and advises the study sponsor regarding the continuing safety of trial subjects, enrollment of potential trial subjects, and the continuing validity and scientific merit of the clinical trial. The data safety monitoring board receives special access to unblinded data during the clinical trial and may advise the sponsor to halt the clinical trial if it determines there is an unacceptable safety risk for subjects or on other grounds, such as no demonstration of efficacy.

The manufacture of investigational drugs for the conduct of human clinical trials (and their active pharmaceutical ingredients) is subject to cGMP requirements. Investigational drugs and active pharmaceutical ingredients imported into the United States are also subject to regulation by the FDA relating to their labeling and distribution. Further, the export of investigational drug products outside of the United States is subject to regulatory requirements of the receiving country as well as U.S. export requirements under the FDCA.

In general, for purposes of NDA approval, human clinical trials are typically conducted in three sequential phases, which may overlap or be combined.

- *Phase 1*—Studies are initially conducted in healthy human volunteers or subjects with the target disease or condition and test the product candidate for safety, dosage tolerance, structure-activity relationships, mechanism of action, absorption, metabolism, distribution, and excretion. If possible, Phase 1 trials may also be used to gain an initial indication of product effectiveness.

- *Phase 2*—Controlled studies are conducted in limited subject populations with a specified disease or condition to evaluate preliminary efficacy, identify optimal dosages, dosage tolerance and schedule, possible adverse effects and safety risks, and expanded evidence of safety.

- *Phase 3*—These adequate and well-controlled clinical trials are undertaken in expanded subject populations, generally at geographically dispersed clinical trial sites, to generate enough data to provide statistically significant evidence of clinical efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product. Typically, two Phase 3 trials are required by the FDA for product approval.

The FDA may also require, or companies may conduct, additional clinical trials for the same indication after a product is approved. These so-called Phase 4 studies may be required by the FDA as a condition of approval of the NDA, to be satisfied after approval. The results of Phase 4 studies can confirm the effectiveness of a product candidate and can provide important safety information. In addition to the above traditional kinds of clinical trial data required for the approval of an NDA, the 21st Century Cures Act provides for potential FDA use of different types and sources of data in regulatory decision-making, such as patient experience data, real world evidence for already approved products, and, for appropriate indications sought through supplemental marketing applications, data summaries. Implementation of this law and related initiatives is still in progress and we do not know the extent to which we may in the future be able to utilize these types and sources of data. In the case of a 505(b)(2) NDA, which is a marketing application in which sponsors may rely on investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted, some of the above described studies and preclinical studies may not be required or may be abbreviated. Bridging studies may be needed, however, to demonstrate the applicability of the studies that were previously conducted by other sponsors to the drug that is the subject of the marketing application.

Clinical trials at any phase may not be completed successfully within any specified period, or at all. Regulatory authorities, an IRB, or the sponsor may suspend or discontinue a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk, the clinical trial is not being conducted in accordance with the FDA's or the IRB's requirements, if the drug has been associated with unexpected serious harm to the subjects, or based on evolving business objectives or competitive climate.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product candidate as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality, potency, and purity of the final product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

During the development of a new drug, a sponsor may be able to request a Special Protocol Assessment, or SPA, the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of an efficacy claim as well as preclinical carcinogenicity trials and stability studies. An SPA may only be modified with the agreement of the FDA and the trial sponsor or if the director of the FDA reviewing division determines that a substantial scientific issue essential to determining the safety or efficacy of the drug was identified after the testing began. An SPA is intended to provide assurance that, in the case of clinical trials, if the agreed-upon clinical trial protocol is followed, the clinical trial endpoints are achieved, and there is a favorable risk-benefit profile, the data may serve as the primary basis for an efficacy claim in support of an NDA. However, SPA agreements are not a guarantee of an approval of a product candidate or any permissible claims about the product candidate. In particular, SPAs are not binding on the FDA if, among other reasons, previously unrecognized public health concerns arise during the performance of the clinical trial, other new scientific concerns regarding the product candidate’s safety or efficacy arise, or if the sponsoring company fails to comply with the agreed upon clinical trial protocol.

NDA Submission, Review by the FDA, and Marketing Approval

Assuming successful completion of the required clinical and preclinical testing, the results of product development, including chemistry, manufacturing, and control (CMC) information, non-clinical studies, and clinical trial results, including negative or ambiguous results as well as positive findings, are all submitted to the FDA, along with the proposed labeling, as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee, authorized every five years by Congress under the Prescription Drug User Fee Act, or PDUFA. User fees must be paid at the time of the first submission of the application, even if the application is being submitted on a rolling basis. Product candidates that are designated as orphan drugs, which are further described below, are also not subject to application user fees unless the application includes an indication other than the orphan indication.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA for a new active ingredient, indication, dosage form, dosage regimen, or route of administration must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. . A sponsor who is planning to submit a marketing application for a drug product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration must submit an initial Pediatric Study Plan, or PSP, within 60 days of an End-of-Phase 2 meeting or as may be agreed between the sponsor and the FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from preclinical studies, early phase clinical studies or other clinical development program. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, to ensure that the benefits of the drug outweigh the risks of the drug. The REMS plan could include medication guides, physician communication plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools. An assessment of the REMS must also be conducted at set intervals. Following product approval, a REMS may also be required by the FDA if new safety information is discovered and the FDA determines that a REMS is necessary to ensure that the benefits of the drug continue to outweigh the risks of the drug.

Once the FDA receives an application, it has 60 days to review the NDA to determine if it is substantially complete to permit a substantive review, before it accepts the application for filing. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the NDA.

The FDA has agreed to a set of performance goals and procedures under PDUFA to review 90% of all applications within ten months from the 60 day filing date for its initial review of a standard NDA for a New Molecular Entity, or NME. For non NME standard applications, the FDA has set the goal of completing its review of 90% of all applications within ten months from the submission receipt date. Such deadlines are referred to as the PDUFA date. The PDUFA date is only a goal, thus, the FDA does not always meet its PDUFA dates. The review process and the PDUFA date may also be extended if the FDA requests, or the NDA sponsor otherwise provides, substantial additional information or clarification regarding the submission.

The FDA may refer an application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved, and applications for new molecular entities are generally discussed at advisory committee meetings unless the FDA determines that this type of consultation is not needed under the circumstances.

An advisory committee is typically a panel that includes clinicians and other experts, which review, evaluate, and make a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions and typically follows such recommendations.

The FDA reviews applications to determine, among other things, whether a product is safe and effective for its intended use and whether the manufacturing methods and controls are adequate to assure and preserve the product's identity, strength, quality, safety, potency, and purity. Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured, referred to as a Pre-Approval Inspection. The FDA will not approve an application unless it determines that the manufacturing processes and facilities, including contract manufacturers and subcontractors, are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA the FDA will inspect one or more clinical trial sites to assure compliance with GCPs.

The approval process is lengthy and difficult, and involves numerous FDA personnel assigned to review different aspects of the NDA, and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional preclinical, clinical, chemistry, manufacturing, and control ("CMC"), or other data and information,. Uncertainties can be presented by reviewers' ability to exercise judgment and discretion during the review process. Even if such data and information are submitted, the FDA and may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than an applicant interprets the same data.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a Complete Response Letter, or CRL. If a CRL is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter; withdraw the application; or request an opportunity for a hearing. A CRL indicates that the review cycle of the application is complete and the application is not ready for approval and describes all of the specific deficiencies that the FDA identified in the NDA. A CRL generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA, and may require additional clinical or preclinical testing in order for the FDA to reconsider the application. The deficiencies identified may be minor, for example, requiring labeling changes; or major, for example, requiring additional clinical trials. The FDA has the goal of reviewing 90% of application and efficacy supplement resubmissions in either two or six months for a Class 1 or Class 2 resubmission, respectively. For non-efficacy supplements (i.e., labeling and manufacturing supplements), CDER's goal is to review the supplement within the same length of time (from receipt) as the initial review cycle (excluding an extension caused by a major amendment of the initial supplement).

Even with the submission of additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when the issues identified in a CRL have been addressed and resolved to the FDA's satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the drug for specific indications and with specific prescribing information which was reviewed in connection with the NDA.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings, or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety and efficacy after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may also not approve label statements that are necessary for successful commercialization and marketing.

After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval. The FDA may also withdraw the product approval if compliance with the pre- and post-marketing regulatory standards are not maintained or if problems occur after the product reaches the marketplace. Further, should new safety information arise, additional testing, product labeling, or FDA notification may be required.

505(b)(2) Approval Process

Section 505(b)(2) of the FDCA, provides an alternate regulatory pathway to FDA approval for new or improved formulations or new uses of previously approved drug products. Specifically, Section 505(b)(2) was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act amendments, and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. The applicant may rely, in part, upon the FDA's prior findings of safety and effectiveness for an approved product that acts as the reference listed drug or on published scientific literature, in support of its application. The FDA may also require 505(b)(2) applicants to perform additional studies or measurements to support the changes from the reference listed drug as well as bridging studies to the reference listed drug. The FDA may then approve the new product candidate for all or some of the labeled indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Orange Book Listing

Section 505 of the FDCA describes three types of marketing applications that may be submitted to the FDA to request marketing authorization for a new drug. A section 505(b)(1) NDA is an application that contains full reports of investigations of safety and efficacy. A section 505(b)(2) NDA is an application in which the applicant, in part, relies on investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. Section 505(j) establishes an abbreviated approval process for a generic version of approved drug products through the submission of an Abbreviated New Drug Application, or ANDA. An ANDA provides for marketing of a generic drug product that has the same active ingredients, dosage form, strength, route of administration, labeling, performance characteristics, and intended use, among other things, to a previously approved product. Limited changes must be pre-approved by the FDA via a suitability petition. ANDAs are termed "abbreviated" because they are generally not required to include preclinical and clinical data to establish safety and efficacy. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent to, or performs in the same manner as, the innovator drug through in vitro, in vivo, or other testing. The generic version must deliver the same amount of active ingredients into a subject's bloodstream in the same amount of time as the innovator drug and can often be substituted by pharmacists under prescriptions written for the reference listed drug.

In seeking approval for a drug through an NDA, including a 505(b)(2) NDA, applicants are required to list with the FDA certain patents whose claims cover the applicant's product and method of use. Upon approval of an NDA, each of the patents listed in the application for the drug is then published in *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the Orange Book. These products may be cited by potential competitors in support of approval of an ANDA or 505(b)(2) NDA.

Any applicant who files an abbreviated new drug application, or ANDA, seeking approval of a generic equivalent version of a drug listed in the Orange Book or a 505(b)(2) NDA referencing a drug listed in the Orange Book must make patent certifications to the FDA that (1) no patent information on the drug or method of use that is the subject of the application has been submitted to the FDA; (2) the patent has expired; (3) the date on which the patent has expired and approval will not be sought until after the patent expiration; or (4) the patent is invalid or will not be infringed upon by the manufacture, use, or sale of the drug product for which the application is submitted. The last certification is known as a paragraph IV certification. Generally, the ANDA or 505(b)(2) NDA approval cannot be made effective until all listed patents have expired, except where the ANDA or 505(b)(2) NDA applicant challenges a listed patent through a paragraph IV certification or if the applicant is not seeking approval of a patented method of use. If the applicant does not challenge the listed patents or does not indicate that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application approval will not be made effective until all of the listed patents claiming the referenced product have expired.

If the competitor has provided a paragraph IV certification to the FDA, the competitor must also send notice of the paragraph IV certification to the holder of the NDA for the reference listed drug and the patent owner within 20 days after the application has been accepted for filing by the FDA. The NDA holder or patent owner may then initiate a patent infringement lawsuit in response to the notice of the paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a paragraph IV certification notice prevents the FDA from making the approval of the ANDA or 505(b)(2) application effective until the earlier of 30 months from the date of the lawsuit, expiration of the patent, settlement of the lawsuit, a decision in the infringement case that is favorable to the applicant or such shorter or longer period as may be ordered by a court. This prohibition is generally referred to as the 30-month stay.

In instances where an ANDA or 505(b)(2) NDA applicant files a paragraph IV certification, the NDA holder or patent owners regularly take action to trigger the 30-month stay, recognizing that the related patent litigation may take many months or years to resolve. Thus, approval of an ANDA or 505(b)(2) NDA could be delayed for a significant period of time depending on the patent certification the applicant makes and the reference drug sponsor's decision to initiate patent litigation.

Exclusivity

Market exclusivity provisions under the FDCA can also delay the submission or the approval effective date of certain applications. The FDA provides periods of regulatory exclusivity, which provides the holder of an approved NDA limited protection from new competition in the marketplace for the innovation represented by its approved drug. Five years of exclusivity are available to New Chemical Entities, or NCEs. An NCE is a drug that contains no active moiety that has been approved by the FDA in any other NDA. An active moiety is the molecule or ion excluding those appended portions of the molecule that cause the drug to be an ester, salt, including a salt with hydrogen or coordination bonds, or other noncovalent derivatives, such as a complex, chelate, or clathrate, of the molecule, responsible for the therapeutic activity of the drug substance. During the exclusivity period, the FDA may not accept for review and make an ANDA or a 505(b)(2) NDA approval effective for an application submitted by another company that contains the previously approved active moiety. An ANDA or 505(b)(2) application, however, may be submitted one year before NCE exclusivity expires if a paragraph IV certification is filed.

If a product is not eligible for NCE exclusivity, it may be eligible for three years of exclusivity. Three-year exclusivity is available to the holder of an NDA, including a 505(b)(2) NDA, for a particular condition of approval, or change to a marketed product, such as a new formulation or indication for a previously approved product, if one or more new clinical studies, other than bioavailability or bioequivalence studies, was essential to the approval of the application and was conducted or sponsored by the applicant. This three-year exclusivity period protects against FDA making an ANDAs and 505(b)(2) NDAs for the condition of the new drug's approval effective. As a general matter, the three year exclusivity does not prohibit the FDA from making an approval for ANDAs or 505(b)(2) NDAs effective for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will also not delay the submission or approval effective date of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy. Moreover, even if a product receives a period of exclusivity, a physician may prescribe the reference listed drug or a generic version of the reference listed drug off-label for the same use as the newly approved drug.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory and statutory exclusivity, including the non-patent exclusivity period described above. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the required time frames, whatever statutory or regulatory periods of exclusivity or Orange Book listed patent protection cover the drug are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot make an ANDA or 505(b)(2) application approval effective as a result of regulatory exclusivity or listed patents. Moreover, pediatric exclusivity attaches to all formulations, dosage forms, and indications for products with existing marketing exclusivity or patent life that contain the same active moiety as that which was studied.

The Orphan Drug Act provides incentives for the development of drugs intended to treat rare diseases or conditions, which generally are diseases or conditions affecting less than 200,000 individuals annually in the United States, or affecting more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making the drug available in the United States will be recovered from United States sales. Additionally, sponsors must present a plausible hypothesis for clinical superiority to obtain orphan designation if there is a drug already approved by the FDA that is intended for the same indication and that is considered by the FDA to be the same drug as the already approved drug. This hypothesis must be demonstrated to obtain orphan drug exclusivity. If granted, prior to product approval, Orphan Drug Designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and application user-fee waivers. The tax advantages, however, were recently limited in Congress' recent tax reform efforts. In addition, if a product receives FDA approval for the indication for which it has orphan designation, the product is generally entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including Fast Track designation, Priority Review and Breakthrough designation, that are intended to expedite or simplify the process for the development and FDA review of certain drug products that are intended for the treatment of serious or life threatening diseases or conditions, and demonstrate the potential to address unmet medical needs or present a significant improvement over existing therapy. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

To be eligible for a Fast Track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life threatening disease or condition and demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if the product will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy, safety, or public health factors. If Fast Track designation is obtained, drug sponsors may be eligible for more frequent development meetings and correspondence with the FDA. In addition, the FDA may initiate review of sections of an NDA before the application is complete. This "rolling review" is available if the applicant provides and the FDA approves a schedule for the remaining information. In some cases, a Fast Track product may be eligible for Accelerated Approval or Priority Review.

The FDA may give a Priority Review designation to drugs that are intended to treat serious conditions and, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions. A Priority Review designation means that the goal for the FDA is to review an application within six months, rather than the standard review of ten months under current PDUFA guidelines, of the 60-day filing date for NMEs and within six months of the submission receipt date for non-NMEs. Products that are eligible for Fast Track designation may also be considered appropriate to receive a Priority Review.

Moreover, under the provisions of the Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, a sponsor can request designation of a product candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are eligible for the Fast Track designation features as described above, intensive guidance on an efficient drug development program beginning as early as Phase 1 trials, and a commitment from the FDA to involve senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Post-approval Requirements

Any product manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, as well as other federal and state agencies, including, among other things, requirements related to manufacturing, recordkeeping, and reporting, including adverse experience reporting, drug shortage reporting, and other periodic reporting; product sampling and distribution; advertising; marketing; promotion; certain electronic records and signatures; licensure in certain states for the manufacturing and distribution of drug products; and post-approval obligations imposed as a condition of approval, such as Phase 4 clinical trials, REMS, and surveillance to assess safety and effectiveness after commercialization.

After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval. There are also continuing annual prescription drug program user fee requirements for any approved products. In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies and list their drug products, and are subject to periodic announced and unannounced inspections by the FDA and these state agencies for compliance with cGMP and other requirements, which impose certain procedural and documentation requirements upon the company and third-party manufacturers.

Changes to the manufacturing process are strictly regulated and often require prior FDA approval or notification before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and specifications, and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

The FDA also strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. A company can make only those claims relating to safety and efficacy, purity, and potency that are approved by the FDA. Physicians, in their independent professional medical judgment, may prescribe legally available products for unapproved indications that are not described in the product's labeling and that differ from those tested and approved by the FDA. Pharmaceutical companies, however, are required to promote their drug products only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability, including, but not limited to, criminal and civil penalties under the FDCA and False Claims Act, exclusion from participation in federal healthcare programs, mandatory compliance programs under corporate integrity agreements, debarment, and refusal of government contracts. Recent court decisions have impacted the FDA's enforcement activity regarding off-label promotion in light of First Amendment considerations; however, there are still significant risks in this area in part due to the potential False Claims Act exposure.

The Drug Supply Chain Security Act, or DSCSA imposes obligations on manufacturers of prescription biopharmaceutical products for commercial distribution, regulating the distribution of the products at the federal level, and sets certain standards for federal or state registration and compliance of entities in the supply chain (manufacturers and repackagers, wholesale distributors, third-party logistics providers, and dispensers). The DSCSA preempts previously enacted state pedigree laws and the pedigree requirements of the Prescription Drug Marketing Act, or PDMA. Trading partners within the drug supply chain must now ensure certain product tracing requirements are met that they are doing business with other authorized trading partners; and they are required to exchange transaction information, transaction history, and transaction statements. Further, the DSCSA limits the distribution of prescription pharmaceutical products and imposes requirements to ensure overall accountability and security in the drug supply chain. As of November 27, 2018 product identifier information (an aspect of the product tracing scheme) is required. The distribution of product samples continues to be regulated under the PDMA.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in significant regulatory actions. Such actions may include refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, imposition of a clinical hold or termination of clinical trials, warning letters, untitled letters, cyber letters, modification of promotional materials or labeling, provision of corrective information, imposition of post-market requirements including the need for additional testing, imposition of distribution or other restrictions under a REMS, product recalls, product seizures or detentions, refusal to allow imports or exports, total or partial suspension of production or distribution, FDA debarment, injunctions, fines, consent decrees, corporate integrity agreements, debarment from receiving government contracts and new orders under existing contracts, exclusion from participation in federal and state healthcare programs, restitution, disgorgement, or civil or criminal penalties including fines and imprisonment, and may result in adverse publicity, among other adverse consequences.

Fraud and Abuse, and Transparency Laws and Regulations

Our business activities, including but not limited to research, sales, promotion, distribution, medical education, and other activities following product approval, will be subject to regulation by numerous federal and state regulatory and law enforcement authorities in the United States in addition to the FDA, including potentially the Department of Justice, the Department of Health and Human Services and its various divisions, including the Centers for Medicare & Medicaid Services, or CMS, and the Health Resources and Services Administration, the Department of Veterans Affairs, the Department of Defense, and certain state and local governments. Our business activities must comply with numerous healthcare laws, including but not limited to, anti-kickback and false claims laws and regulations as well as data privacy and security laws and regulations, which are described below.

The federal Anti Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting, or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, furnishing, or order of any item or service reimbursable under Medicare, Medicaid, or other federal healthcare programs, in whole or in part. The term "remuneration" has been interpreted broadly to include anything of value. The Anti Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, formulary managers, and beneficiaries on the other. There are certain statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. The exceptions and safe harbors are drawn narrowly, and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case by case basis based on a cumulative review of all of its facts and circumstances to determine whether one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business. The Patient Protection and Affordable Care Act, or ACA, of 2010, as amended, modified the intent requirement under the Anti Kickback Statute to a stricter standard, such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, a violation of the federal Anti Kickback Statute may be grounds for the government or a whistleblower to assert that a claim for payment of items or services resulting from such violation constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Certain Anti-Kickback safe harbor provisions that protect the rebates paid by drug manufacturers to third parties may be repealed pursuant to a pending regulatory proposal.

The government has asserted false claims act liability against manufacturers by alleging that improper arrangements with ordering physicians caused them or another provider to file false claims in violation of the False Claims Act or that manufacturers' support of patient assistance programs improperly induced beneficiaries to choose their products in violation of the civil monetary penalty statute. Sales, marketing and business arrangements in the healthcare industry are also subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs, patient assistance programs, and other business arrangements. Medicare Advantage and Medicaid managed care plan regulations prohibit certain forms of marketing to enrollees that are designed to discriminate against beneficiaries on the basis of their health conditions or history. These regulations may require regulatory review of marketing materials, and coordination with health plan or governmental regulators.

The ACA further created new federal requirements for reporting under the Physician Payments Sunshine Act, or the Sunshine Act, by applicable manufacturers of covered drugs, payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members. 2018 legislation extended the Sunshine Act to cover payments and transfers of value to physician assistants, nurse practitioners, and other mid-level practitioners (with reporting requirements going into effect in 2022 for payments and transfers of value made in 2021). Beyond the ACA, financial arrangements and incentives that may impact healthcare decision-making continue to be a subject of attention for Congress and health regulators. For example, the federal Eliminating Kickbacks in Recovery Act of 2018 (EKRA) notably in some instances (relating to recovery centers, clinical treatment facilities, and clinical laboratories) applies to services payable by commercial insurers and self-pay patients, as opposed to only services for which payment is available from government payors.

The federal civil False Claims Act, or FCA, prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment to, or approval by, the federal government, knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or avoiding, decreasing, or concealing an obligation to pay money to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. The civil False Claims Act has been used to assert liability on the basis of kickbacks and other improper referrals, improperly reported government pricing metrics such as Best Price or Average Manufacturer Price, or submission of inaccurate information required by government contracts, improper use of Medicare provider or supplier numbers when detailing a provider of services, improper promotion of off-label uses not expressly approved by the FDA in a drug's label, and allegations as to misrepresentations with respect to the products supplied or services rendered. Several pharmaceutical and other healthcare companies have further been sued under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Intent to deceive is not required to establish liability under the civil False Claims Act; however, a November 2017 Department of Justice memorandum now prohibits the use of subregulatory guidance documents to impose new or more stringent requirements on entities outside the Executive Branch of the federal government. Because the Department has experienced recent administration changes, it is unclear whether the new Attorney General will continue this policy. Civil False Claims Act actions may be brought by the government or may be brought by private individuals on behalf of the government, called "qui tam" actions. If the government decides to intervene in a qui tam action and prevails in the lawsuit, the individual will share in the proceeds from any fines or settlement funds. If the government declines to intervene, the individual may pursue the case alone, subject to governmental review and certain approvals. Qui tam complaints are filed under seal, and the cases may progress for a number of years before a complaint is unsealed and a manufacturer becomes aware of its existence. Since 2004, these False Claims Act lawsuits against pharmaceutical companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements, as much as $3.0 billion, regarding certain sales practices and promoting off-label drug uses. For example, Civil False Claims act liability may be imposed for Medicare or Medicaid overpayments arising out of claims that were filed by providers but alleged to have been caused by manufacturers' incentives, impermissible discounts, overpayments caused by understated rebate amounts, and overpayments that are retained for more than 60 days after discovering the overpayment. False claims act enforcement may also arise from claims filed as the result of manufacturing marketing materials that contained inaccurate statements or provided certain reimbursement guidance.

The government may further prosecute conduct constituting a false claim under the criminal False Claims Act. The criminal False Claims Act prohibits the making or presenting of a claim to the government knowing such claim to be false, fictitious, or fraudulent and, unlike the civil False Claims Act, requires proof of intent to submit a false claim. Similarly, the criminal healthcare fraud statute imposes criminal liability for, among other things, knowingly and willfully attempting or executing a scheme to defraud any healthcare benefit program, including private third-party payors, obtaining money or property of a benefit program by false or fraudulent means, or falsifying, concealing, or covering up a material fact or submitting a materially false statement in connection with the delivery of, or payment form healthcare benefits, items, or services.

The civil monetary penalties statute is another potential statute under which biopharmaceutical companies may be subject to enforcement. Among other things, the civil monetary penalties statue imposes fines against any person who is determined to have presented, or caused to be presented, claims to a federal healthcare program that the person knows, or should know, is for an item or service that was not provided as claimed or is false or fraudulent.

The exclusion statute requires the exclusion of entities and individuals who have been convicted of federal-program related crimes or health care felony fraud or controlled substance charges. The statute also permits the exclusion of those that have been convicted of any form of fraud, the anti-kickback statute, for obstructing an investigation or audit, misdemeanor controlled substance charges, those whose health care license has been revoked or suspended, and those who have filed claims for excessive charges or unnecessary services. If a company were to be excluded, its products would be ineligible for reimbursement from any federal programs, including Medicare and Medicaid, and no other entity participating in those programs would be permitted to enter into contracts with the company. In order to preserve access to beneficial drugs, the government may elect to exclude officers and key employees of manufacturers, rather than excluding the organization. Such enforcement actions would prohibit the Company from engaging those individuals, which could adversely affect operations, and could result in significant reputational harm.

Payment or reimbursement of prescription drugs by Medicaid or Medicare requires manufacturers of the drugs to submit pricing information to CMS. The Medicaid Drug Rebate statute requires manufacturers to calculate and report price points, which are used to determine Medicaid rebate payments shared between the states and the federal government and Medicaid payment rates for certain drugs. For drugs paid under Medicare Part B, manufacturers must also calculate and report their Average Sales Price, which is used to determine the Medicare Part B payment rate for the drug. Drugs that are approved under a Biologic License Application, or BLA, or an NDA, including 505(b)(2) drugs, are subject to an additional inflation penalty which can substantially increase rebate payments. In addition, for BLA and NDA drugs, the Veterans Health Care Act, or VHCA, requires manufacturers to calculate and report to the Veterans Administration, or VA, a different price called the Non-Federal Average Manufacturing Price, which is used to determine the maximum price that can be charged to certain federal agencies, referred to as the Federal Ceiling Price, or FCP. Like the Medicaid rebate amount, the FCP includes an inflation penalty. A Department of Defense regulation requires manufacturers to provide this discount through prescription rebates on drugs dispensed by retail pharmacies when paid by the TRICARE Program. All of these price reporting requirements create risk of submitting false information to the government, and potential FCA liability.

The VHCA also requires manufacturers of covered drugs participating in the Medicaid program to enter into Federal Supply Schedule contracts with the VA through which their covered drugs must be sold to certain federal agencies at FCP and to report pricing information. This necessitates compliance with applicable federal procurement laws and regulations and subjects us to contractual remedies as well as administrative, civil, and criminal sanctions. In addition, the VHCA requires manufacturers participating in Medicaid to agree to provide different mandatory discounts to certain Public Health Service grantees and other safety net hospitals and clinics, and report the ceiling price to the Health Resources and Services Agency within Health and Human Services.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, a healthcare benefit program, regardless of whether the payor is public or private, knowingly and willfully embezzling or stealing from a health care benefit program, willfully obstructing a criminal investigation of a health care offense, and knowingly and willfully falsifying, concealing, or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items, or services relating to healthcare matters. The ACA, as amended, modified the intent requirement under the certain portions of these federal criminal statutes such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it.

Further, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its respective implementing regulations, imposes certain requirements on covered entities relating to the privacy, security, and transmission of individually identifiable health information. Among other things, HITECH, through its implementing regulations, makes HIPAA's security standards and certain privacy standards directly applicable to business associates, defined as a person or organization, other than a member of a covered entity's workforce, that performs certain functions or activities that involve the use or disclosure of protected health information on behalf of, or provides services to, a covered entity. HITECH also strengthened the civil and criminal penalties that may be imposed against covered entities, business associates, and individuals, 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. In addition, other federal and state laws may govern the privacy and security of health and other 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.

Even for entities that are not deemed "covered entities" or "business associates" under HIPAA, according to the United States Federal Trade Commission, or the FTC, failing to take appropriate steps to keep consumers' personal information secure constitutes unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act, or the FTCA, 15 USC § 45(a). The FTC expects a company's data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities. Medical data is considered sensitive data that merits stronger safeguards. The FTC's guidance for appropriately securing consumers' personal information is similar to what is required by the HIPAA Security Rule.

In addition, other federal and state laws may govern the privacy and security of health and other 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. For example, California recently enacted legislation – the California Consumer Privacy Act, or CCPA, which goes into effect January 1, 2020. The CCPA, among other things, creates new data privacy obligations for covered companies and provides new privacy rights to California residents, including the right to opt out of certain disclosures of their information. The CCPA also creates a private right of action with statutory damages for certain data breaches, thereby potentially increasing risks associated with a data breach. Legislators have stated that they intend to propose amendments to the CCPA before it goes into effect, and the California Attorney General will issue clarifying regulations. It remains unclear what, if any, modifications will be made to this legislation or how it will be interpreted. The effects of the CCPA potentially are significant, however, and may require us to modify our data processing practices, and may cause us to incur substantial costs and expenses to comply. Although the law includes certain limited exceptions, including for information collected as part of clinical trials as specified in the law, it remains unclear what, if any, modifications will be made to this legislation or how it will be interpreted.

Many states have also adopted laws similar to each of the above federal laws, which may be broader in scope and apply to items or services reimbursed by any third-party payor, including commercial insurers, and some have transparency laws that require reporting price increases and related information. Certain state laws also regulate manufacturers' use of prescriber-identifiable data. Certain states also require implementation of commercial compliance programs and compliance with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or otherwise restrict payments or the provision of other items of value that may be made to healthcare providers and other potential referral sources; impose restrictions on marketing practices; or require drug manufacturers to track and report information related to payments, gifts, and other items of value to physicians and other healthcare providers. These laws may affect our future sales, marketing, and other promotional activities by imposing administrative and compliance burdens.

If our operations are found to be in violation of any of the laws or regulations described above or any other laws that apply to us, we may be subject penalties or other enforcement actions, including criminal and significant civil monetary penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government healthcare programs, corporate integrity agreements, debarment from receiving government contracts or refusal of new orders under existing contracts, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Coverage and Reimbursement Generally

The commercial success of our product candidates and our ability to commercialize any approved product candidates successfully will depend in part on the extent to which governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers, and other third-party payors provide coverage for and establish adequate reimbursement levels for our product candidates. Government authorities, private health insurers, and other organizations generally decide which drugs they will pay for and establish reimbursement levels for healthcare. Medicare is a federally funded program managed by the Centers for Medicare and Medicaid Services, or CMS, through local contractors that administer coverage and reimbursement for certain healthcare items and services furnished to the elderly and disabled. Medicaid is an insurance program for certain categories of patients whose income and assets fall below state-defined levels and who are otherwise uninsured that is both federally and state funded and managed by each state. The federal government sets general guidelines for Medicaid and each state creates specific regulations that govern its individual program, including supplemental rebate programs that prioritize coverage for drugs on the state Preferred Drug List. Similarly, government laws and regulations establish the parameters for coverage of prescription drugs by Tricare, the health care program for military personnel, retirees, and related beneficiaries. Many states have also created pharmacy assistance programs for individuals who do not qualify for federal programs. In the United States, private health insurers and other third-party payors often provide reimbursement for products and services based on the level at which the government provides reimbursement through the Medicare or Medicaid programs for such products and services.

In the United States, the European Union, and other potentially significant markets for our product candidates, government authorities and third-party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. For example, in the United States, federal and state governments reimburse covered prescription drugs at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of healthcare services and products. Third-party payors are developing increasingly sophisticated methods of controlling healthcare costs. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication. Third-party payors also control costs by requiring prior authorization or imposing other dispensing restrictions before covering certain products and by broadening therapeutic classes to increase competition. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. Absent clinical differentiators, third-party payors may treat products as therapeutically equivalent and base formulary decisions on net cost. To lower the prescription cost, manufacturers frequently rebate a portion of the prescription price to the third-party payors.

Federal programs also impose price controls through mandatory ceiling prices on purchases by federal agencies and federally funded hospitals and clinics and mandatory rebates on retail pharmacy prescriptions paid by Medicaid and Tricare. These restrictions and limitations influence the purchase of healthcare services and products. Legislative proposals to reform healthcare or reduce costs under government programs may result in lower reimbursement for our product candidates or exclusion of our product candidates from coverage. In addition, government programs like Medicaid include substantial penalties for increasing commercial prices over the rate of inflation which can affect realization and return on investment.

Private payors often rely on the lead of the governmental payors in rendering coverage and reimbursement determinations. Therefore, achieving favorable CMS coverage and reimbursement is usually a significant gating issue for successful introduction of a new product. In addition, many government programs as a condition of participation mandate fixed discounts or rebates from manufacturers regardless of formulary position or utilization, and then rely on competition in the market to attain further price reductions, which can greatly reduce realization on the sale.

Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the European Union will put additional pressure on product pricing, reimbursement, and utilization, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups and health technology assessment bodies, competition within therapeutic classes, availability of generic equivalents, judicial decisions and governmental laws and regulations related to Medicare, Medicaid, and healthcare reform, pharmaceutical coverage and reimbursement policies, and pricing in general. Patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Sales of our product candidates will therefore depend substantially, both domestically and abroad, on the extent to which the costs of our products will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, such as Medicare and Medicaid, private health insurers, and other third-party payors.

As a result of the above, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA and other comparable foreign regulatory authority approvals. Our product candidates may not be considered medically necessary or cost-effective, or the rebate percentages required to secure coverage may not yield an adequate margin over cost.

There is often pressure to renegotiate pricing and reimbursement levels, including, in particular, in connection with changes to Medicare. Third-party payors continue to demand discounted fee structures, and the trend toward consolidation among third-party payors tends to increase their bargaining power over price structures. If third-party payors reduce their rates for our products, then our revenue and profitability may decline and our operating margins will be reduced. Because some third-party payors rely on all or portions of Medicare payment systems to determine payment rates, changes to government healthcare programs that reduce payments under these programs may negatively impact payments from third-party payors. Our inability to maintain suitable financial arrangements with third-party payors could have a material adverse impact on our business. Additionally, the reimbursement process is complex and can involve lengthy delays. Third party payors may disallow, in whole or in part, providers' requests for reimbursement based on determinations that certain amounts are not reimbursable under plan coverage, that the drugs provided were not medically necessary, or that additional supporting documentation is necessary. Retroactive adjustments may change amounts realized from third party payors. Delays and uncertainties in the reimbursement process may adversely affect market acceptance and utilization of our products, resulting in reduced revenues. The unavailability or inadequacy of third-party coverage and reimbursement could negatively affect the market acceptance of our products and the future revenues we may expect to receive from those products. In addition, we are unable to predict what additional legislation or regulation relating to the healthcare industry or third-party coverage and reimbursement may be enacted in the future, or what effect such legislation or regulation would have on our business. Many hospitals implement a controlled and defined process for developing and approving formularies. Any marketing efforts that are determined to have violated such policies could result in the denial or removal of our products from that hospital's formulary.

Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our products and product candidates or exclusion of our products and product candidates from coverage. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates. We cannot provide any assurances that we will be able to obtain and maintain third-party coverage or adequate reimbursement for our product candidates in whole or in part.

In early 2019, the U.S. Department of Health and Human Services published a rule package that proposes to eliminate the Anti-Kickback Statute safe harbor protection for rebates paid by drug manufacturers to pharmacy benefit managers, Medicare Part D plans, and Medicaid managed care plans. The proposed regulation would also create new safe harbors for fees charged to manufacturers by pharmacy benefit managers and for drug discounts offered to patients at the point of sale. If adopted, these rule amendments are expected to cause significant changes throughout the drug supply chain, and could affect our business operations and prospects in unknown and material ways.

Healthcare Reform Measures

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals designed to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality, and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

For example, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or MMA, established a new prescription drug benefit program for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Part D plans include both standalone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, which do not utilize formularies to restrict coverage, Part D coverage varies by plan. With some exceptions, Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for any products for which we receive marketing approval. However, Part D plans use competition for coverage to leverage manufacturer rebates. Further, the law requires manufacturers to absorb a significant percentage of the prescription price paid for NDA drugs, including 504(b)(2) drugs, during a beneficiary's coverage gap. The Bipartisan Budget Act of 2018 permanently increased manufacturer liability for the prescription price in the coverage gap from 50% to 70% beginning in 2019, while simultaneously accelerating closure of the gap. These cost reduction initiatives and other provisions of the legislation, as well as any negotiated price discounts for our future products covered by a Part D prescription drug plan, may decrease the coverage and reimbursement rate that we receive, lower the net price realized on our sales to pharmacies, or both. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-governmental payors.

The ACA established the Patient-Centered Outcome Research Institute to organize and coordinate federally funded research to compare the effectiveness of different treatments for the same illness. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates. If third-party payors do not consider our product candidates to be cost-effective compared to other available therapies, they may not cover our product candidates, once approved, as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The ACA made other changes intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health care industry, and impose additional health policy reforms. The law expanded the eligibility criteria for Medicaid programs, thereby potentially increasing both the volume of sales and manufacturers' Medicaid rebate liability. The law also expanded the entities eligible for discounts under the 340B drug discount program, which mandates discounts to certain hospitals, community centers, and other qualifying providers, although, with the exception of children's hospitals, these newly eligible entities are not eligible to receive discounted 340B pricing on orphan drugs and the Health Resources and Services Administration has narrowed its interpretation of which beneficiaries may fill prescriptions through 340B inventories. The law additionally extended manufacturer's Medicaid rebate liability to covered drugs dispensed to patients enrolled in Medicaid managed care organizations, increased the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate program, and created an alternative rebate formula for certain new formulations of certain existing products, which is intended to increase the amount of rebates due on those drugs. The revisions to the Medicaid rebate formula can have the further effect of increasing the required 340B discounts. Finally, the ACA imposes a significant annual fee on companies that manufacture or import branded prescription drug products. Substantial new provisions affecting compliance have also been enacted through the ACA and otherwise, including the reporting of drug sample distribution, which may require us to modify our business practices with healthcare practitioners. Moreover, in the coming years, additional changes could be made to governmental healthcare programs that could significantly impact the success of our product candidates.

The ACA also imposed an affirmative obligation to report and repay any overpayments, including those payments that resulted from violations of the Anti-Kickback Statute, false claims act, or civil monetary penalties statute, within sixty (60) days after such overpayment has been identified. Corresponding case law imposes an obligation on entities to exercise reasonable diligence in identifying such overpayments. The failure to timely report and repay is, itself, considered to constitute a violation of the False Claims Act.

The cost of pharmaceuticals continues to generate substantial governmental and third party payor interest, and pharmaceutical pricing and marketing currently received a great deal of Congressional and administrative attention. Some states, such as California, have enacted transparency laws that require manufacturers to report drug price increases and related information. In addition, for example, in 2018 CMS proposed a new rule that if finalized would require direct-to-consumer television advertisements of prescription drugs, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug. We expect that the pharmaceutical industry will experience pricing pressures due to the trend toward managed healthcare, the increasing influence of managed care organizations, judicial interpretation of health care reform efforts, and additional legislative and regulatory proposals resulting in ongoing, relatively rapid changes to applicable laws and regulations. Our results of operations could be adversely affected by current and future healthcare reforms.

Government and private payors also increasingly require pre-approval of coverage for new or innovative devices or drug therapies or condition coverage on unsuccessful alternative treatment before they will reimburse healthcare providers that use such therapies. For some specialty drugs, payors are conditioning payment on successful treatment measured by objective metrics. While we cannot predict whether any proposed cost-containment measures will be adopted or otherwise implemented in the future, the announcement or adoption of these proposals could have a material adverse effect on our ability to obtain adequate prices for our product candidates and operate profitably.

Other legislative changes have been proposed and adopted since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011, as amended, reduced funding under certain conditions to several government programs, including aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which remain in effect through 2027 unless additional Congressional action is taken. The Center for Medicare and Medicaid Services has promulgated or amended a number of cost containment and value based reimbursement measures in the ordinary course of business, and it is expected to continue revising its regulations and policies in response to market conditions and administrative directives.

Since January 2017, Congress and the Trump Administration have been engaged in various efforts to repeal or materially modify various aspects of ACA. The results and effects of such ongoing efforts have varied after facing judicial and Congressional challenges, but could affect our business operations and prospects in unknown ways, and it is unclear how ACA and other laws ultimately will be implemented. For example, the United States District Court for the Northern District of Texas struck down the ACA, deeming it unconstitutional given that Congress repealed the individual mandate in 2017. This decision has been stayed pending outcome of an appeal to the Fifth Circuit Court of Appeals.

In the future, there may continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit the prices we will be able to charge for our product candidates, or the amounts of reimbursement available for our product candidates. If future legislation were to impose direct governmental price controls or access restrictions, it could have a significant adverse impact on our business. Managed care organizations, as well as Medicaid and other government agencies, continue to seek price discounts. Some states have implemented, and other states are considering, measures to reduce costs of the Medicaid program, and some states are considering implementing measures that would apply to broader segments of their populations that are not Medicaid-eligible. Due to the volatility in the current economic and market dynamics, we are unable to predict the impact of any unforeseen or unknown legislative, regulatory, payor or policy actions, which may include cost containment and healthcare reform measures. Such policy actions could have a material adverse impact on our profitability.

These and other healthcare reform initiatives may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on our financial operations. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party, or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. Activities that violate the FCPA, even if they occur wholly outside the United States, can result in criminal and civil fines, imprisonment, disgorgement, oversight, and debarment from government contracts.

Foreign Regulation

To the extent we choose to develop or sell any products outside of the United States, we will be subject to a variety of foreign regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales, and distribution of our products. For example, in the European Union, or EU, we must obtain authorization of a clinical trial application in each member state in which we intend to conduct a clinical trial prior to the pending introduction of a EU portal for EU-wide approvals. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary greatly from country to country. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. As in the United States, post-approval regulatory requirements, such as those regarding product manufacture, marketing, or distribution, would apply to any product that is approved outside the United States.

European Union Drug Approval Process

To obtain a marketing authorization of a drug in the European Union, we may submit marketing authorization applications, or MAAs, either under the so-called centralized, decentralized, mutual recognition, or national authorization procedures.

Centralized Procedure

The centralized procedure provides for the grant of a single marketing authorization following a favorable opinion by the European Medicines Agency, or EMA, that is valid in all European Union member states, as well as Iceland, Liechtenstein, and Norway. The centralized procedure is compulsory for medicines produced by specified biotechnological processes, products designated as orphan medicinal products, and products with a new active substance indicated for the treatment of specified diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders, or autoimmune diseases and other immune dysfunctions. The centralized procedure is optional for products that represent a significant therapeutic, scientific, or technical innovation, or whose authorization would be in the interest of public health. Under the centralized procedure the maximum timeframe for the evaluation of an MAA by the EMA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee of Medicinal Products for Human Use, or the CHMP. Accelerated assessment might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. The timeframe for the evaluation of an MAA under the accelerated assessment procedure is of 150 days, excluding clock stops.

Authorization Procedures

There are also two other possible routes to authorize medicinal products in several European Union countries, which are available for investigational medicinal products that fall outside the scope of the centralized procedure:

- *Decentralized procedure.* Using the decentralized procedure, an applicant may apply in more than one European Union country, although the applicant must nominate one reference European Union Member State, for simultaneous authorization of medicinal products that have not yet been authorized in any European Union country and that do not fall within the mandatory scope of the centralized procedure. Failing agreement, there is a procedure for resolving disagreements between member states and ultimately an arbitration procedure before the CHMP.

- *Mutual recognition procedure.* In the mutual recognition procedure, a medicine is first authorized in one European Union Member State, referred to as the reference member state, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other nominated European Union countries, referred to as the concerned member states, in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization. The procedure for disagreements described above similarly applies.

- *National procedures.* Purely national procedures continue to be possible but are strictly limited to where the product is to be authorized in one member state only.

In the European Union, new products authorized for marketing, referred to as reference products, qualify for eight years of data exclusivity and an additional two years of market exclusivity upon marketing authorization. The data exclusivity period prevents generic applicants from relying on the preclinical and clinical trial data contained in the dossier of the reference product when applying for a generic marketing authorization in the European Union during a period of eight years from the date on which the reference product was first authorized in the European Union. The market exclusivity period prevents a successful generic applicant from commercializing its product in the European Union until 10 years have elapsed from the initial authorization of the reference product in the European Union. The 10-year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

Research and Development

Conducting research and development is central to our business model. We have invested and expect to continue to invest significant time and capital in our research and development operations. Our research and development expenses were $23.5 million, $20.0 million, and $21.2 million for the years ended December 31, 2018, 2017, and 2016, respectively. We plan to increase our research and development expenses for the foreseeable future as we seek to complete the development of AXS-05, AXS-07, AXS-09, AXS-12, AXS-02, and AXS-06.

Employees

As of March 11, 2019, we had 29 full-time employees. None of our employees is represented by a collective bargaining agreement and we have never experienced any work stoppage. We believe that we maintain good relations with our employees.

Corporate Information

We were incorporated in Delaware in January 2012. Our offices are located at 25 Broadway, 9th Floor, New York, New York 10004, and our telephone number is (212) 332-3241.

Available Information

We file reports and other information with the SEC, as required by the Exchange Act. We make available free of charge through our website (http://www.axsome.com) our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled “Investors,” as a source of information about us. The foregoing references to our website are not intended to, nor shall they be deemed to, incorporate information on our website into this Annual Report on Form 10-K by reference.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the "JOBS Act". We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our initial public offering in November 2015, (b) in which we have total annual gross revenue of at least $1.07 billion, or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeded $700 million as of the prior June 30th, and (2) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

ITEM 1A. RISK FACTORS.

Investing in our common stock involves a high degree of risk. You should carefully consider the risk factors set forth below as well as the other information contained in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes and the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations." Any of the following risks could materially and adversely affect our business, financial condition or results of operations. The risks described below are not the only risks facing us. Additional risks and uncertainties not currently known to us or that we currently view to be immaterial may also materially adversely affect our business, financial condition or results of operations. In these circumstances, the market price of our common stock would likely decline.

RISKS RELATED TO OUR FINANCIAL CONDITION AND CAPITAL REQUIREMENTS

We have incurred significant losses since our inception, anticipate that we will incur substantial and increasing losses for the foreseeable future, and may never achieve or maintain profitability.

We are a clinical stage biopharmaceutical company with a limited operating history. For the last several years, we have focused our efforts primarily on developing CNS product candidates AXS-02, AXS-05, AXS-06, AXS-07, AXS-09, and AXS-12, which we refer to herein as our product candidates, with the goal of achieving regulatory approval. Since inception, we have incurred significant operating losses. Our net losses were $31.0 million and $28.9 million for the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018, we had an accumulated deficit of $107.6 million. To date, we have not received regulatory approvals for any of our product candidates or generated any revenue from the sale of products, and we do not expect to generate any revenue in the foreseeable future. We expect to continue to incur substantial and increasing expenses and operating losses over the next several years, as we continue to develop our current and future product candidates. In addition, we expect to incur significant sales, marketing, and manufacturing expenses related to the commercialization of our current and future product candidates, if they are approved by the U.S. Food and Drug Administration, or FDA. As a result, we expect to continue to incur significant losses for the foreseeable future. We anticipate that our expenses will increase substantially as we:

- conduct our Phase 3 clinical trials with AXS-05 for the treatment of depression;
- conduct our Phase 3 clinical trials with AXS-05 for the treatment of agitation associated with Alzheimer's disease, or AD agitation;
- conduct our Phase 3 clinical trials with AXS-07 for the acute treatment of migraine;
- conduct our Phase 2 clinical trials with AXS-12 in narcolepsy;
- continue to evaluate, plan for, and conduct, clinical trials for AXS-05 for smoking cessation treatment and AXS-09 for the treatment of CNS disorders;
- continue to evaluate, plan for, and conduct, clinical trials for our Axsome PPC product candidates, including AXS-02 for the treatment of pain associated with knee osteoarthritis, or OA, associated with bone marrow lesions, or BMLs and AXS-06 for the treatment of osteoarthritis and rheumatoid arthritis;
- develop, in-license, or acquire additional product candidates;
- conduct late-stage clinical trials for any product candidates that successfully complete early-stage clinical trials;
- seek regulatory approval for any product candidates that successfully complete late-stage clinical trials;

- conduct additional non-clinical studies with any product candidates;
- conduct clinical studies with any additional product candidates;
- increase manufacturing batch sizes of our product candidates to satisfy FDA requirements for a marketing application submission;
- establish a sales, marketing, and distribution infrastructure, and scale up external manufacturing capabilities to commercialize any products for which we may obtain regulatory approval and that we choose not to license to a third party;
- require larger quantities of product;
- maintain, expand, and protect our intellectual property portfolio;
- hire additional clinical, quality control, and scientific personnel; and
- add operational, financial, and management information systems and personnel, including personnel to support our product candidate development and planned future commercialization efforts.

To become and remain profitable, we must succeed in developing and eventually commercializing products that generate significant revenue. We do not expect to generate significant revenue unless and until we are able to obtain marketing approval for and successfully commercialize one or more of our product candidates. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates and manufacturing, marketing, and selling any products for which we may obtain regulatory approval, achieving market acceptance of our products, satisfying any post-marketing requirements, maintaining appropriate distribution, setting prices, and obtaining reimbursement for our products from private insurance or government payors. We are only in the preliminary stages of some of these activities. We may never succeed in these activities and, even if we do, may never achieve profitability.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses we may incur or when, or if, we will be able to achieve profitability. If we are required by the FDA or comparable foreign regulatory authorities to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings, or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We will need additional funding to conduct our future clinical trials and to complete development and commercialization of our product candidates. If we are unable to raise capital when needed, we would be forced to delay, reduce, or eliminate our product development programs or commercialization efforts.

Conducting clinical trials, pursuing regulatory approvals, establishing outsourced manufacturing relationships, and successfully manufacturing and commercializing our product candidates, is, and will be, a very time-consuming, expensive, and uncertain process that takes years to complete. We will need to raise additional capital to:

- fund our future clinical trials for our current product candidates, especially if we encounter any unforeseen delays or difficulties in our planned development activities;
- fund our operations and continue our efforts to hire additional personnel and build a commercial infrastructure to prepare for the commercialization of our current and future product candidates, if approved by the FDA or other comparable foreign regulatory authorities;
- qualify and outsource the commercial-scale manufacturing of our products under current good manufacturing practices, or cGMP;
- develop additional product candidates; and
- in-license other product candidates.

We believe our current cash, which includes proceeds from the January 2019 at-the-market equity financings and the March 2019 term loan, will be sufficient to fund our anticipated operating cash requirements into at least the fourth quarter of 2021. We have based this estimate on assumptions that may prove to be wrong and we could spend our available financial resources faster than we currently expect. Further, we may not have sufficient financial resources to meet all of our objectives if any product candidate is approved, which could require us to postpone, scale back, or eliminate some, or all, of these objectives, including our potential launch activities relating to our product candidates. Our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress and costs related to the development of our product candidates;
- the costs associated with conducting additional non-clinical studies with any of our product candidates;
- the potential for delays in our efforts to seek regulatory approval for our product candidates, and any costs associated with such delays;
- the costs of establishing a commercial organization to sell, market, and distribute our product candidates;
- the rate of progress and costs of our efforts to prepare for the submission of a new drug application, or NDA, for any product candidates that we may in-license or acquire in the future, and the potential that we may need to conduct additional clinical or preclinical trials to support applications for regulatory approval;
- the costs of filing, prosecuting, defending, and enforcing any patent claims and other intellectual property rights associated with our product candidates;
- the cost and timing of manufacturing sufficient supplies of our product candidates in preparation for commercialization;
- the effect of competing technological and market developments;
- revenue, if any, received from commercial sales of our product candidates, subject to the receipt of regulatory approval;
- the terms and timing of any collaborative, licensing, co-promotion, or other arrangements that we may establish; and
- the success of the commercialization of any of our current or future product candidates.

Future capital requirements will also depend on the extent to which we acquire or invest in additional businesses, products, and technologies. Until we can generate a sufficient amount of product revenue, if ever, we expect to finance future cash needs through public or private equity offerings, debt financings, royalties, and corporate collaboration and licensing arrangements, as well as through interest income earned on cash and investment balances. We cannot be certain that additional funding will be available on acceptable terms, or at all. If adequate funds are not available, we may be required to delay, reduce the scope of, or eliminate one or more of our development programs or our commercialization efforts.

Our operating activities may be restricted as a result of covenants related to the outstanding indebtedness under our loan agreement and we may be required to repay the outstanding indebtedness in an event of default, which could have a materially adverse effect on our business.

In March 2019, we entered into a loan and security agreement with SVB and WestRiver Innovation Lending Fund VIII, L.P. consisting of an initial $20.0 million tranche, which was funded shortly upon closing, with the remaining $4.0 million available to be drawn, at our option, subject to the achievement of positive data, on or prior to August 15, 2019, with respect to our ongoing Phase 2 clinical trial for AXS-12 in narcolepsy, sufficient to submit a Phase 3 protocol to the FDA, provided that we have not received any objections from the FDA within thirty days after submission of such Phase 3 protocol. A portion of the first tranche was used to satisfy our existing obligations under our original term loan facility with SVB, as amended, and such obligations are considered fully repaid and extinguished. The new term loan facility matures in February 2023 and has an interest-only monthly payment period for twelve months, which may be extended to 18 months upon drawing of the second tranche. Following the interest-only payment period, we will begin making monthly payments of principal and interest until the maturity date. Interest will accrue on the unpaid principal balance of the outstanding loan advances at a floating per annum rate equal to the greater of (i) seven and one-half of one percent (7.50%) and (ii) two percent (2.0%) above the prime rate.

The loan subjects us to various customary covenants, including requirements as to financial reporting and insurance, and restrictions on our ability to dispose of our business or property, change our line of business, liquidate or dissolve, enter into any change in control transaction, merge or consolidate with any other entity or acquire all or substantially all the capital stock or property of another entity, incur additional indebtedness, incur certain types of liens on our property, including our intellectual property, pay any dividends or other distributions on our capital stock other than dividends payable solely in capital stock or redeem our capital stock. Our business may be adversely affected by these restrictions on our ability to operate our business.

Additionally, we may be required to repay the outstanding indebtedness under the SVB Loan if an event of default occurs under the SVB Loan. Under the SVB Loan, an event of default will occur if, among other things, we fail to make payments under the SVB Loan; we breach any of our covenants under the SVB Loan, subject to specified cure periods with respect to certain breaches; we or our assets become subject to certain legal proceedings, such as bankruptcy proceedings; we are unable to pay our debts as they become due; or we default on contracts with third parties which would permit SVB to accelerate the maturity of such indebtedness or that could have a material adverse effect on us. We may not have enough available cash or be able to raise additional funds through equity or debt financings to repay such indebtedness at the time any such event of default occurs. In that case, we may be required to delay, limit, reduce or terminate our product candidate development or commercialization efforts or grant to others rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. SVB could also exercise its rights as collateral agent to take possession and dispose of the collateral securing the loan for its benefit, which collateral includes all of our property other than our intellectual property. Our business, financial condition and results of operations could be materially adversely affected as a result of any of these events. Our management has broad discretion in the application of the proceeds from the SVB Loan, subject to the covenants and limitations described in the SVB Loan.

We have a limited operating history and no history of commercializing products, which may make it difficult to evaluate our business and prospects.

We commenced operations in 2012, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, and developing our product candidates, including undertaking preclinical studies and conducting clinical trials of our product candidates. We have not yet demonstrated an ability to obtain regulatory approval for, or successfully commercialize, a product candidate. In addition, as a relatively nascent business, we may encounter unforeseen expenses, difficulties, complications, delays, and other known and unknown difficulties. If our product candidates are approved by the FDA, we will need to expand our capabilities to support commercial activities. We may not be successful in adding such capabilities. Consequently, any predictions about our future performance may not be as accurate as they could be if we had a history of successfully developing and commercializing pharmaceutical products.

RISKS RELATED TO OUR BUSINESS AND THE DEVELOPMENT OF OUR PRODUCT CANDIDATES

We are substantially dependent on the success of our product candidates and cannot guarantee that any of our product candidates will successfully complete any planned or ongoing Phase 3 clinical trials, receive regulatory approval, or be successfully commercialized.

We currently have no products approved for commercial distribution. We have invested a significant portion of our efforts and financial resources in the development of our product candidates. Our business depends entirely on the successful development and commercialization of our product candidates, which may never occur. Our ability to generate revenues in the near term is substantially dependent on our ability to develop, obtain regulatory approval for, and then successfully commercialize our product candidates. We currently generate no revenues from sales of any products, and we may never be able to develop or commercialize a marketable product. Furthermore, given the nature of our business, the biopharmaceutical industry in general and the uncertainty and costs associated with developing our product candidates within a complicated and costly regulatory regime, our goals, plans and assumptions with respect to our product candidates may evolve or change. For example, we may not continue to emphasize, focus our research and development efforts on or direct resources to certain of our product candidates, and we may shift our focus and resources to our other current or future product candidates. Any such change in our business strategy could harm our business, cause uncertainty or confusion in the marketplace or harm the clinical prospects of our product candidates.

Our product candidates will require additional clinical and non-clinical development, regulatory approval, commercial manufacturing arrangements, establishment of a commercial organization, significant marketing efforts, and further investment before we generate any revenues from product sales. We initiated our Phase 3 clinical trial with AXS-02 for the treatment of the pain of knee OA associated with BMLs in March 2016, our Phase 3 clinical trial with AXS-05 for the treatment of TRD in March 2016, our Phase 2/3 trial with AXS-05 for the treatment of agitation associated with AD in July 2017, our Phase 2 with AXS-05 trial for the treatment of MDD in June 2018, our Phase 2 trial with AXS-12 for the treatment of narcolepsy in January 2019, and our Phase 3 trial with AXS-07 for the acute treatment of migraine in March 2019. As a result of one or more risks discussed in this section, we cannot assure you that we will meet projected timelines related to these trials.

We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates. Even if our product candidates are approved, they may be subject to limitations on the indicated uses for which they may be marketed, distribution restrictions, or to other conditions of approval, may contain significant safety warnings, including boxed warnings, contraindications, and precautions, may not be approved with label statements necessary or desirable for successful commercialization, or may contain requirements for costly post-market testing and surveillance, or other requirements, including the submission of a risk evaluation and mitigation strategy, or REMS, to monitor the safety or efficacy of the products. If we do not receive regulatory approval for, and successfully commercialize, our product candidates, we will not be able to generate revenue from these product

candidates in the foreseeable future, or at all. Any significant delays in obtaining approval for and commercializing our product candidates will have a material adverse impact on our business and financial condition.

We have not previously submitted an NDA to the FDA, or similar drug approval filings to comparable foreign authorities, for any product candidate, and we cannot be certain that our current or future product candidates will be successful in clinical trials or receive regulatory approval. Moreover, we have only completed limited early stage studies with our product candidates to date. For AXS-05, we completed three Phase 1 pharmacokinetic studies and one Phase 2 trial in MDD. For AXS-07, we have only conducted one Phase 1 clinical trial. For AXS-09, we have only completed one Phase 1 clinical trial. Finally, for AXS-12, we recently initiated a Phase 2 study. For AXS-02, we have only completed one Phase 1 clinical trial. Furthermore, we have only conducted one Phase 1 pharmacokinetic study for our product candidate AXS-06 and additional manufacturing work is required before we may submit an investigational new drug application, or IND, and begin late-stage clinical trials.

Our product candidates are susceptible to the risks of failure inherent at any stage of product development, including the appearance of unexpected adverse events or failure to achieve its primary endpoints in subsequent clinical trials, including our initiated and planned Phase 3 clinical trials. For example, in January 2018, we conducted an interim analysis for our then-ongoing Phase 3 trial of AXS-02 for the treatment of CRPS, which we referred to as the CREATE-1 trial, and for our currently ongoing Phase 3 trial of AXS-02 for the treatment of the pain of knee OA associated with BMLs, which we refer to as the COAST-1 trial. Based on the recommendation we received from the independent data monitoring committee, we will continue our COAST-1 trial and have discontinued our CREATE-1 trial for futility. We paused screening in the COAST-1 trial prior to the conduct of the interim analysis for that trial and do not plan to resume screening and enrollment in the COAST-1 trial until after the final data readout from our STRIDE-1 trial. We conducted one interim analysis for the ongoing Phase 3 trial of AXS-05 in TRD and for the ongoing Phase 2/3 trial of AXS-05 for the treatment of AD agitation. We may elect to conduct interim analyses for our other clinical trials. Interim results of a clinical trial do not necessarily predict final results, and interim results may result in early stoppage of our clinical trials for futility or modifications to our clinical trials, including the addition of additional subjects. Further, our product candidates may not receive regulatory approval even if they are successful in clinical trials.

If approved for marketing by applicable regulatory authorities, our ability to generate revenues from our product candidates depend on our ability to:

- create market demand for our product candidates through our own marketing and sales activities, and any other arrangements to promote these product candidates that we may otherwise establish;
- receive regulatory approval for claims that are necessary or desirable for successful marketing;
- hire, train, and deploy a sales force to commercialize our product candidates in the United States;
- manufacture our product candidates in sufficient quantities and at acceptable quality and manufacturing cost to meet commercial demand at launch and thereafter;
- establish and maintain agreements with wholesalers, distributors, and group purchasing organizations on commercially reasonable terms;
- create partnerships with, or offer licenses to, third parties to promote and sell our product candidates in foreign markets where we receive marketing approval;
- maintain patent and trade secret protection and regulatory exclusivity for our product candidates;
- launch commercial sales of our product candidates, whether alone or in collaboration with others;

- achieve market acceptance of our product candidates by patients, the medical community, and government and private third-party payors;
- achieve appropriate reimbursement for our product candidates;
- effectively compete with other therapies; and
- maintain a continued acceptable safety profile of our product candidates following launch.

Potential conflicts of interest exist with respect to the intellectual property rights that we license from an entity owned by our Chief Executive Officer and Chairman of the Board, and it is possible that our interests and their interests may diverge.

In 2012, we entered into three exclusive license agreements with Antecip Bioventures II LLC, or Antecip, an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which we were granted exclusive licenses to develop, manufacture, and commercialize Antecip's patents and applications related to the development of our current product candidates. Although Dr. Tabuteau dedicates all of his working time to us because Antecip is an inactive intellectual property holding company, he may face potential conflicts of interest regarding these licensing transactions as a result of his ownership of Antecip. The license agreements provide that, subject to the reasonable consent of Antecip, we have the right to control the prosecution or defense, as the case may require, of a patent infringement claim involving the licensed intellectual property. Our interests with respect to pleadings and settlements in such cases may be at odds with those of Antecip. If there is a dispute between us and Antecip, Dr. Tabuteau will have a conflict of interest because he may, at the time of a prospective dispute, simultaneously have a financial interest in and owe a fiduciary duty to Antecip and simultaneously have a financial interest in and owe a fiduciary duty to us. For example, if a contractual dispute arises between us and Antecip under any of the license agreements we have with Antecip, Dr. Tabuteau may be in a position where he would benefit if Antecip prevails, to the detriment of our business or our investors, even though he is an officer and director of our company, because he is the sole owner of Antecip. Similarly, if we have a claim of any kind against Antecip, Dr. Tabuteau may be, even as our Chief Executive Officer and Chairman of the Board, reluctant to assert a claim by us against Antecip because of his financial interest in Antecip. We cannot assure you that any conflicts will be resolved in our favor, and as a result, our business could be impeded or materially harmed.

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.

Because we have limited financial and managerial resources, we focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both its regulatory approval and commercialization. As such, we are currently primarily focused on the development of AXS-05 for the treatment of depression, agitation associated with AD, and smoking cessation, AXS-07 for the acute treatment of migraine and AXS-12 for the treatment of narcolepsy. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. Additionally, as more fully described in "Business—Material License Agreements," we are required to pay to an entity owned by our Chief Executive Officer and Chairman of the Board certain royalty payments related to the development of AXS-02 and AXS-05, as well as AXS-04, a product candidate that is currently in early-stage development, but not with respect to the development of other product candidates, which may influence management's decision concerning which product candidates or indications to pursue. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products 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 products. 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 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.

Our future growth may depend on our ability to identify and develop product candidates and if we do not successfully identify and develop product candidates or integrate them into our operations, we may have limited growth opportunities.

A component of our business strategy is to continue to develop a pipeline of product candidates by developing products that we believe are a strategic fit with our focus on central nervous system, or CNS, therapeutics. However, these business activities may entail numerous operational and financial risks, including:

- difficulty or inability to secure financing to fund business activities for such development;
- disruption of our business and diversion of our management's time and attention;
- higher than expected development costs;
- exposure to unknown liabilities;
- difficulty in managing multiple product development programs; and
- inability to successfully develop new products or clinical failure.

For instance, our prior efforts have resulted in our decision not to further develop certain product candidates that, at one time, appeared to be promising. We have limited resources to identify and execute the developments of products. Moreover, we may devote resources to potential development that are never completed, or we may fail to realize the anticipated benefits of such efforts. If we do not successfully develop and commercialize product candidates, we may not be able to obtain product revenues in future periods.

If safety and efficacy data for our product candidates, a reference listed drug, or published literature does not satisfactorily demonstrate safety and efficacy to the FDA, or if the FDA and other regulators do not permit us to rely on the data of a reference listed drug or published literature, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We are not permitted to commercialize, market, promote, or sell any product candidate in the United States without obtaining marketing approval from the FDA. Comparable foreign regulatory authorities, such as the European Medicines Agency, or EMA, impose similar restrictions.

In the United States, we currently plan to at least initially seek approval of our product candidates using the 505(b)(2) pathway. The FDA interprets Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, or FDCA, for purposes of approving an NDA, to permit the applicant to rely, in part, upon published literature or the FDA's previous findings of safety and efficacy for an approved product. The FDA, though, requires companies to perform additional clinical trials or preclinical studies to support any deviation from the previously approved product and to support reliance on the FDA's prior findings of safety and efficacy or published literature.

Under the 505(b)(2) pathway, the FDA may approve our product candidates for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought pursuant to the Section 505(b)(2) process. The label, however, may require all or some of the limitations, contraindications, warnings, or precautions included in the reference product's label, including a box warning (commonly referred to as a "black box warning"), or may require additional limitations, contraindications, warnings, or precautions, including class-wide warnings. For instance, antidepressants, including bupropion, include a class-wide black box warning regarding the increased risk of suicidal thoughts and behavior.

Based on the side effects disclosed in FDA product labels for marketed drugs that contain the same active molecule as our product candidate, AXS-02 may result in nausea, fatigue, anemia, bone pain, constipation, fever,

vomiting, dyspnea, hypersensitivity reactions, osteonecrosis of the jaw, renal toxicity, musculoskeletal pain, atypical fractures, hypocalcemia, bronchoconstriction, or other adverse events or potential adverse events reported or discussed in the product labels for zoledronic acid-containing products including Zometa, Reclast, and Aclasta.

Based on the side effects disclosed in FDA product labels for marketed drugs that contain the same active molecules as our product candidate, AXS-05 may result in dry mouth, nausea, insomnia, dizziness, pharyngitis, abdominal pain, agitation, anxiety, tremor, seizure, increase in blood pressure and heart rate, hepatoxicity, hypoglycemia, thrombocytopenia or other hypersensitivity reactions, QRS prolongation, left ventricular hypertrophy or left ventricular dysfunction, palpitation, sweating, tinnitus, myalgia, anorexia, urinary frequency, rash, seizure, hypertension, activation of mania or hypomania, psychosis and other neuropsychiatric reactions, suicidal ideation, suicide attempt, completed suicide, angle closure glaucoma, allergic or anaphylactoid or anaphylactic reactions, diarrhea, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased gamma-glutamyltransferase, flatulence, or other adverse events or potential adverse events reported or discussed in the product labels for bupropion-containing products or dextromethorphan-containing products including Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban, Contrave, and Nuedexta.

Based on the side effects disclosed in FDA product labels for marketed drugs that contain the same active molecules as our product candidate, AXS-07 may result in fatigue, confusion, dry mouth, diarrhea, nausea, insomnia, anemia, increased appetite, anxiety, sweating, dizziness, palpitations, arrythmia, tachycardia, abnormal vision, syncope, seizure, tremor, tinnitus, dizziness, somnolence, paresthesia, dysgeusia, dyspepsia, constipation, weight increase or decrease, gastritis, hematuria, flatulence, esophagitis, gastric ulcers, gastroesophageal reflux, gastrointestinal hemorrhages, colitis, rash, pain or tightness in the chest, neck, throat or jaw, upper respiratory tract infections, influenza-like symptoms, or other adverse events or potential adverse events reported or discussed in the product labels for meloxicam containing or rizatriptan-containing products including Vivlodex, Mobic, and Maxalt.

Based on the side effects disclosed in EMA product label for marketed drugs that contain the same active molecule as our product candidate, AXS-12 may result in decreased appetite, insomnia, agitation, anxiety, dizziness, headache, paraesthesia, akathisia, dysgeusia, accommodation disorder, mydriasis, glaucoma, vertigo, tachycardia, palpitations, vasodilation, hypotension, hypertension, dry mouth, vomiting, hyperhidrosis, rash, sensation of incomplete bladder emptying, urinary tract infection, dysuria, urinary retention, erectile dysfunction, ejaculatory pain, ejaculatory delay, chills, or other adverse events or potential adverse events reported or discussed in the product labels for reboxetine containing products including Edronax.

In addition, because we plan to file our product candidates under an NDA submitted pursuant to 505(b)(2), we will rely, at least in part, upon a reference listed drug and published literature. For example, we intend to rely on data collected in certain investigator-initiated Phase 2 clinical trials and other third-party studies in the published literature as well as FDA findings of safety and efficacy for approved drug products containing the same active molecules in AXS-02 and AXS-05. If the FDA disagrees with our conclusions regarding the appropriateness of our reliance on a reference listed drug or published literature, we could be required to conduct additional clinical trials or other studies to support our NDA, which could lead to unanticipated costs and delays or to the termination of our development program. If we are unable to obtain approval for our pharmaceutical formulations through the 505(b)(2) NDA process, we may be required to pursue the more expensive and time-consuming 505(b)(1) approval process, which consists of full reports of investigations of safety and effectiveness conducted by or for the applicant. In addition, because we plan to submit NDAs for AXS-02 and AXS-05 pursuant to the 505(b)(2) process, we have not conducted Phase 2 clinical trials for these product candidates and, as such, we will have less experience with actual testing of the product candidate.

There may also be circumstances under which the FDA would not allow us to pursue a 505(b)(2) application. For instance, should the FDA approve a pharmaceutically equivalent product to our product candidates, before we obtain approval, we would no longer be able to use the 505(b)(2) pathway. In that case, it is the FDA's policy that the appropriate submission would be an Abbreviated New Drug Application, or ANDA, for a generic version of the approved product. We may, however, not be able to immediately submit an ANDA or have an ANDA approval made effective, as we could be blocked by others' periods of patent and regulatory exclusivity protection.

Notwithstanding the approval of a number of products by the FDA under 505(b)(2) over the last few years, pharmaceutical companies and others have objected to the FDA's interpretation of Section 505(b)(2). If the FDA's interpretation of Section 505(b)(2) is successfully challenged, the FDA may change its policies and practices with respect to Section 505(b)(2) regulatory approvals, which could delay or even prevent the FDA from approving any NDA that we submit pursuant to the 505(b)(2) process. Moreover, our inability to pursue a 505(b)(2) application could result in new competitive products reaching the market more quickly than our product candidates, which could hurt our competitive position and our business prospects.

We may never receive approval for any of our product candidates, and even if our product candidates are approved under 505(b)(2), the approval may be subject to limitations on the indicated uses for which the products may be marketed, distribution restrictions, or to other conditions of approval; may contain significant safety warnings, including boxed warnings, contraindications, and precautions; may not be approved with label statements necessary or desirable for successful commercialization; or may contain requirements for costly post-market testing and surveillance or other requirements, including REMS, to monitor the safety or efficacy of the products. Moreover, any future actions or inquiries by the FDA with respect to the reference listed drug may require that we make changes to our labeling, discontinue development, or, possibly, withdraw the product from the market.

An NDA submitted under Section 505(b)(2) subjects us to the risk that we may be subject to a patent infringement lawsuit or regulatory actions that would delay or prevent the review or approval of our product candidate.

Applicants submitting NDAs under Section 505(b)(2) of the FDCA must provide a patent certification with the application for all reference listed drugs and for all brand name products identified in published literature upon which the 505(b)(2) application relies. One such certification is known as a paragraph IV certification, which certifies that any patents listed in the FDA's publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book, are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the product that is the subject of the 505(b)(2) NDA.

Under the Hatch-Waxman Act, the holder of patents or NDAs that the 505(b)(2) application references may file a patent infringement lawsuit after receiving notice of the paragraph IV certification. Filing of a patent infringement lawsuit against the filer of the 505(b)(2) applicant within 45 days of the patent or NDA owner's receipt of notice triggers a one-time, automatic, 30-month stay of the FDA's ability to make the 505(b)(2) NDA approval effective. In such a case, the FDA may not make the 505(b)(2) NDA approval effective until the earlier of 30 months from the receipt of the notice of the paragraph IV certification, the expiration of the patent, when the infringement case concerning each such patent was favorably decided in the applicant's favor or settled, or such shorter or longer period as may be ordered by a court. Accordingly, we may invest a significant amount of time and expense in the development of one or more product candidates only to be subject to significant delay and patent litigation before such product candidates may be commercialized, if at all. In addition, a 505(b)(2) application approval will not be made effective until any existing non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, or NCE, or exclusivities for changes to NCEs listed in the Orange Book for the referenced product have expired or, if possible, are carved out from the label.

Companies that produce branded reference listed drugs routinely bring litigation against applicants that seek regulatory approval to manufacture and market generic and reformulated forms of their branded products. These companies often allege patent infringement or other violations of intellectual property rights as the basis for filing suit. Likewise, patent holders may bring patent infringement suits against companies that are currently marketing and selling their approved generic or reformulated products. Litigation to enforce or defend intellectual property rights is often complex and often involves significant expense and can delay or prevent introduction or sale of our product candidates. If patents are held to be valid and infringed by our product candidates in a particular jurisdiction, we may be required to cease selling, relinquish or destroy existing stock, or pay monetary damages in that jurisdiction unless we can obtain a license from the patent holder. There may also be situations where we use our business judgment and decide to market and sell our approved products, notwithstanding the fact that allegations of patent infringement(s) have not been finally resolved by the courts, which is known as an "at-risk launch." The risk involved in doing so can be substantial because

the remedies available to the owner of a patent for infringement may include, among other things, damages measured by the profits lost by the patent owner which may be greater than the profits earned by the infringer. In the case of willful infringement, such damages may be increased up to three times. An adverse decision in patent litigation could have a material adverse effect on our business, financial position, and results of operations and could cause the market value of our common stock to decline. Should we need to file a paragraph IV certification in the future for our product candidates, we may risk patent litigation and substantial delays.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming, and inherently unpredictable. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates as expected, and our ability to generate revenue will be materially impaired.

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions, and may require us to amend our clinical trial protocols or conduct additional studies that require regulatory or institutional review board, or IRB, approval, or otherwise cause delays in the approval or rejection of an application. We have not obtained regulatory approval for any product candidate and it is possible that none of our existing product candidates, or any product candidates we may seek to develop in the future, will ever obtain regulatory approval. Any delay in obtaining or failure to obtain required approvals could materially adversely affect our ability or that of any of our collaborators to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States, and by the EMA and similar regulatory authorities outside the United States and Europe. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have no experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations, or CROs, and consultants to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy for that indication. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities and clinical trial sites by, the regulatory authorities.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies; our product candidates' mechanism of action; studies conducted by third parties in different patient populations, using different products, or using different study designs; and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. Preclinical studies may also reveal unfavorable product candidate characteristics, including safety concerns. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Our future clinical trial results may not be successful. Moreover, should there be a flaw in a clinical trial, it may not become apparent until the clinical trial is well advanced.

We may also experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- regulators or IRBs may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site or amend trial protocols;

- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites and our CROs;
- clinical trials of our product candidates may produce negative or inconclusive results, or our studies may fail to reach the necessary level of statistical or clinical significance, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- interim analyses may result in our clinical trials being discontinued for safety or futility reasons or may result in modifications to our clinical trials that prolong the trials or make them difficult and more expensive to complete, such as increases in the number of subjects;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or the clinical trial protocol, or meet their contractual obligations to us in a timely manner, or at all, or we may be required to engage in additional clinical trial site monitoring;
- we, the regulators, or IRBs may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks, undesirable side effects, or other unexpected characteristics of the product candidate, or due to findings of undesirable effects caused by a chemically or mechanistically similar drug or drug candidate. We may also discontinue clinical research and programs due to changing business priorities;
- changes in marketing approval policies during the development period rendering our data insufficient to obtain marketing approval;
- changes in or the enactment of additional statutes or regulations;
- changes in regulatory review for each submitted product application;
- the cost of clinical trials of our product candidates may be greater than we anticipate or we may have insufficient funds for a clinical trial or to pay the substantial user fees required by the FDA upon the filing of an NDA;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- we may decide, or regulators may require us, to conduct additional clinical trials, analyses, reports, data, or preclinical trials than we currently plan, or we may abandon product development programs. For instance, with respect to our ongoing Phase 3 clinical trial with AXS-02 for the treatment of the pain of knee OA associated with BMLs, although we have received a Special Protocol Assessment, or SPA, the FDA stated that if there is a recurrence of knee OA pain, we will need to explore repeat dosing, which would require additional preclinical studies. Further, for AXS-05, we will need to conduct additional clinical and preclinical studies in addition to our Phase 3 and Phase 2/3 trials in order to file an NDA for this product candidate. Additionally, although we believe that we may be able to rely on a single pivotal study to support our NDA for AXS-07 for the acute treatment of migraine, the FDA may ultimately disagree and require us to conduct additional pivotal studies. Finally, for AXS-12, we will need to conduct additional clinical studies in addition to our newly initiated Phase 2 trial in order to file an NDA for this product candidate. The outcome of our studies may further necessitate additional clinical or preclinical work;

- we may fail to reach an agreement with regulators regarding the scope or design of our clinical trials;
- we may have delays in adding new investigators or clinical trial sites, or we may experience a withdrawal of clinical trial sites;
- patients that enroll in our studies may misrepresent their eligibility or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the study or clinical trial, increase the needed enrollment size for the study or clinical trial, or extend the study's or clinical trial's duration;
- there may be regulatory questions regarding interpretations of data and results, or new information may emerge regarding our product candidates;
- the FDA or comparable foreign regulatory authorities may disagree with our study design or our interpretation of data from preclinical studies and clinical trials or find that a product candidate's benefits do not outweigh its safety risks. For instance, in our communications with the FDA, the FDA has raised questions and had comments regarding our preclinical studies and clinical trials, such as comments on the acceptability of the proposed trial designs for our product candidates, the number of patients planned for our studies, our data analysis plans, the applicability of the serum biomarkers studied in our Phase 1 study of AXS-02, the species and doses used in our preclinical studies, and the results of our preclinical studies;
- the FDA or comparable foreign regulatory authorities may disagree with our belief that certain product attributes are advantageous or may require further study of product attributes that are different than our reference listed drugs. For instance, while we believe that certain of the pharmacokinetic results for AXS-06 are favorable, the FDA may disagree, refuse labeling claims based upon these results, or determine that additional studies are necessary to substantiate the benefits. Pharmacokinetic differences between our product candidates and the reference listed drugs, may also make bridging studies more difficult or may prevent us from using the 505(b)(2) pathway. If we are prevented from using the 505(b)(2) pathway, we will need to use the more time consuming and expensive NDA pathway to receive product approval;
- the FDA or comparable foreign regulatory authorities may not accept data from studies with clinical trial sites in foreign countries;
- the FDA or comparable foreign regulatory authorities may disagree with our intended indications;
- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or our manufacturing facilities for clinical and future commercial supplies;
- the FDA or comparable foreign regulatory authorities may take longer than we anticipate to make a decision on our product candidates; and
- we may not be able to demonstrate that a product candidate provides an advantage over current standards of care or current or future competitive therapies in development.

Moreover, if we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials or other testing of our product candidates, if the results of these trials or tests are not positive, or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;

- obtain approval for indications or patient populations that are not as broad as intended or desired or are not covered by our intellectual property;

- obtain approval with labeling that includes significant use or distribution restrictions, including restrictions on the intended patient population, or safety warnings, including boxed warnings, contraindications, and precautions, or may not include label statements necessary or desirable for successful commercialization;

- be subject to additional post-marketing testing and surveillance requirements, including REMS; or

- have the product removed from the market after obtaining marketing approval.

Our product candidate development costs will also increase if we experience delays in testing or approvals and we may not have sufficient funding to complete the testing and approval process for any of our product candidates. We may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our product candidates. We do not know whether any additional preclinical tests or clinical trials will be required, will begin as planned, will need to be restructured, or will be completed on schedule, or at all. Significant delays relating to any preclinical studies or clinical trials also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors, or the competitors of our collaborators, to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that cause, or lead to, such delays may ultimately lead to the denial of marketing approval of any of our product candidates. If any of this occurs, our business, financial condition, results of operations, and prospects will be materially harmed.

Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical studies, clinical trials, or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit, or prevent marketing approval of a product candidate. . During the course of review, the FDA may also request or require additional chemistry, manufacturing, and control (CMC), or other data and information, and the development and provision of these data and information may be time consuming and expensive. Furthermore, there is the possibility that the FDA or comparable foreign regulatory authorities have not previously reviewed product candidates for the indications we are pursuing, such as bisphosphonates for the treatment of pain. As a result, we may experience delays in regulatory approval due to uncertainties in the approval process.

Finally, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications or uses than we request, may contain significant safety warnings, including black box warnings, contraindications, and precautions, may grant approval contingent on the performance of costly post-marketing clinical trials, surveillance, or other requirements, including REMS to monitor the safety or efficacy of the product, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of these scenarios could compromise the commercial prospects for our product candidates.

If we experience delays in obtaining approval, if we fail to obtain approval of a product candidate or if the label for a product candidate does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate, the commercial prospects for such product candidate may be harmed and our ability to generate revenues from that product candidate will be materially impaired.

The FDA may determine that any of our current or future product candidates have undesirable side effects that could delay or prevent their regulatory approval or commercialization.

Undesirable side effects caused by our product candidates could cause us, IRBs, and other reviewing entities or regulatory authorities to interrupt, delay, or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. For example, if concerns are raised

regarding the safety of a new drug as a result of undesirable side effects identified during clinical or preclinical testing, the FDA may order us to cease further development, decline to approve the drug, or issue a letter requesting additional data or information prior to making a final decision regarding whether or not to approve the drug.

The number of requests for additional data or information issued by the FDA in recent years has increased, and resulted in substantial delays in the approval of several new drugs. Undesirable side effects caused by any of our current or future product candidates could also result in denial of regulatory approval by the FDA or other comparable foreign authorities for any or all targeted indications or the inclusion of unfavorable information in our product labeling, such as limitations on the indicated uses for which the products may be marketed or distributed, a label with significant safety warnings, including boxed warnings, contraindications, and precautions, a label without statements necessary or desirable for successful commercialization, or may result in requirements for costly post-marketing testing and surveillance, or other requirements, including REMS, to monitor the safety or efficacy of the products, and in turn prevent us from commercializing and generating revenues from the sale of any of our current or future product candidates.

To date, the most commonly reported adverse events observed in the completed clinical trial of AXS-02 include headache, fever, musculoskeletal pain, diarrhea, abdominal pain, nausea, myalgia, and chills. Some reported adverse events led to discontinuation from our trial of AXS-02. These adverse events included abdominal pain.

To date, the most commonly reported adverse events observed in a completed clinical trial with zoledronic acid, the active molecule in AXS-02, for the treatment of the pain of knee OA associated with BMLs include acute phase reactions, primarily cold or flu-like symptoms and headaches.

To date, the most commonly reported adverse events observed in a completed clinical trial with zoledronic acid, the active molecule in AXS-02, for the treatment of CLBP associated with MCs include fever, headache, myalgia, arthralgia, pain, nausea, and flu-like symptoms. Sinusitis requiring temporary hospitalization following zoledronic acid infusion was reported in one patient and was therefore classified as a serious adverse event.

To date, the most commonly reported adverse events observed in the completed clinical trials of the combination of DM, one of the active molecules in AXS-05, and quinidine for the treatment of pseudobulbar affect and agitation in patients with probable AD include falls, dizziness, headache, nausea, diarrhea, and urinary tract infection.

To date, the most commonly reported adverse events observed in the completed clinical trials of AXS-05 include headache, nausea, dizziness, insomnia, dry mouth, fatigue, hypoesthesia, disturbance in attention, hyperhidrosis, increased heart rate, palpitation, constipation, diarrhea, increased blood pressure, and tremor. Some reported adverse events resulted in discontinuations from our trials of AXS-05. These adverse events included chest pain, headache, abdominal pain, diarrhea, signs of potential allergic reactions, atrial tachycardia, disturbance in attention, metamorphosia, tremor, feeling hot, dizziness, dyspnea, and increased respiratory rate. AXS-05 consists of DM and bupropion, and this combination may exacerbate any known adverse events for each individual component, or may result in new toxicities as compared to those of the individual components.

If any of our other product candidates is associated with serious adverse events or undesirable side effects or have properties that are unexpected, we may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe, or more acceptable from a risk-benefit perspective. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may significantly harm our business, financial condition, results of operations, and prospects.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue conducting clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the United States. Some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Patient enrollment is affected by other factors including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the eligibility criteria for, and design of, the clinical trial in question, including factors such as frequency of required assessments, length of the study, and ongoing monitoring requirements;
- the perceived risks and benefits of the product candidate under study, including the potential advantages or disadvantages of the product candidate being studied in relation to other available therapies;
- competition in recruiting and enrolling patients in clinical trials;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- effectiveness of publicity created by clinical trial sites regarding the trial;
- patients' ability to comply with the specific instructions related to the trial protocol, proper documentation, and use of the drug product;
- inability to obtain or maintain patient informed consents;
- risk that enrolled patients will drop out before completion;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays which would cause us to miss our projected timelines and could require us to abandon one or more clinical trials altogether. For instance, because we are seeking regulatory approval for certain indications that may have a narrow or small patient population, it may be difficult to find patients eligible to participate in our clinical studies at a sufficient rate or in a sufficient quantity. For our initiated Phase 3 clinical trial with AXS-02 for the treatment of the pain of knee OA associated with BMLs and our planned Phase 3 clinical trial in CLBP associated with type 1 or mixed type 1 and type 2 MCs, enrollment will require the existence of radiographic biomarkers, we may require patients to discontinue use of their existing medication before participating in our clinical trials, and we may exclude patients with advanced disease. In addition, for our planned Phase 3 clinical trial with AXS-02 in CLBP associated with type 1 or mixed type 1 and type 2 MCs, we will exclude women of childbearing potential from our potential patient population. We may also exclude patients who have been treated with opioids or other classes of medications. For our Phase 3 clinical trial with AXS-05 for the treatment of TRD, we are requiring patients to have previously failed one or two antidepressant treatments, which further limits our potential patient population. For our Phase 2/3 clinical trial with AXS-05 for the

treatment of agitation associated with AD, we exclude patients who have been treated with certain classes of medications. For our Phase 3 clinical trial with AXS-07 for the acute treatment of migraine, only patients with a history of inadequate response to prior migraine treatments will be enrolled. As a result, these and other entry criteria may make it difficult for us to enroll patients in any of our clinical trials. We may be required by the FDA to modify the entry criteria for our ongoing or planned Phase 3 clinical trials and these changes may make it more difficult to enroll patients in our clinical trials. Moreover, patients in our clinical trials, especially patients in our control groups, may be at risk for dropping out of our studies if they are not experiencing relief of their symptoms. A significant number of withdrawn patients would compromise the quality of our data.

Enrollment delays in our clinical trials may result in increased development costs for our product candidates, or the inability to complete development of our product candidates, which would cause the value of our company to decline, limit our ability to obtain additional financing, and materially impair our ability to generate revenues.

Currently approved products containing bupropion are subject to restrictive marketing and distribution regulations, which if applied to our product candidates would restrict their use and harm our ability to generate profits.

Some of the currently approved products containing the same active ingredients as our product candidates require medication guides. Medication guides can be required independently or as part of REMS programs. REMS programs, in addition to medication guides, may require special communication plans to healthcare professionals, or elements to assure safe use, such as restricted distribution methods, distribution only to certain medical professionals, training for medical professionals prescribing our product candidates, patient registries, or other risk minimization tools. The FDA may determine that our product candidates will require a REMS program or medication guide. We cannot predict whether either will be required as part of the FDA's approval of our product candidates and, if required, what those requirements might be. Any limitations on approval or marketing could restrict the commercial promotion, distribution, prescription, or dispensing of our product candidates, if approved. If a REMS program is required, depending on the extent of the REMS requirements, the program might significantly increase our costs to commercialize these product candidates or could place a substantial burden on medical professionals, discouraging their use of our product candidates, if approved. Furthermore, risks of our product candidates that are not adequately addressed through proposed REMS or medication guides for such product candidates may also prevent or delay their approval for commercialization.

Development of combination product candidates may present more or different challenges than development of a single-agent product candidate.

Certain of our product candidates, including AXS-05, AXS-06, AXS-07, and AXS-09 are combination therapies. A combination therapy is a single drug product that consists of two or more active ingredients, with each component making a contribution to the claimed effect of the drug. The development of combination drugs may be more complex than the development of single agent products and generally requires that sponsors demonstrate the contribution of each component to the claimed effect and the safety and efficacy of the product as a whole. This requirement may make the design and conduct of clinical trials more complex, requiring more clinical trial subjects. We also may not be able to meet the FDA's approval standards required for combination products. Finally, the FDA's requirements concerning combination products may change in the future. Moreover, the applicable requirements for approval may differ from country to country.

Changes in product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates are developed through preclinical studies to late-stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. For instance, two of our initial studies of AXS-05 were completed with two separate tablets containing DM and bupropion. Our Phase 3 studies, however, are being conducted using a single tablet containing both active ingredients. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform

differently and affect the results of planned clinical trials or other future clinical trials conducted with the altered materials. Such changes may also require additional testing, FDA notification, or FDA approval. This could delay completion of clinical trials; require the conduct of bridging clinical trials or studies, or the repetition of one or more clinical trials; increase clinical trial costs; delay approval of our product candidates; and jeopardize our ability to commence product sales and generate revenue.

Failure to obtain marketing approval in international jurisdictions would prevent our product candidates from being marketed abroad.

In order to market and sell our products in the European Union, or EU, and many other jurisdictions, we or our third-party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or these third parties may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, the failure to obtain approval in one jurisdiction may compromise our ability to obtain approval elsewhere. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

A Fast Track product designation or other designation to facilitate product candidate development may not lead to faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We have received a Fast Track product designation for AXS-02 for the treatment of the pain of knee OA associated with BMLs, and for AXS-05 for both the treatment of TRD as well as for the treatment of agitation associated with AD, and we may seek Fast Track designation for other of our current or future product candidates. Receipt of a designation to facilitate product candidate development is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for a designation, the FDA may disagree. In any event, the receipt of such a designation for a product candidate may not result in a faster development process, review, or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate marketing approval by the FDA. In addition, the FDA may later decide that the products no longer meet the designation conditions.

Regulatory approval is limited by the FDA or comparable foreign regulatory authorities to those specific indications and conditions for which clinical safety and efficacy have been demonstrated, and we may be subject to fines, penalties, injunctions, or other enforcement actions if we are determined to be promoting the use of our products for unapproved or "off-label" uses, resulting in damage to our reputation and business.

We, and any of our collaborators, must comply with requirements concerning advertising and promotion for any of our product candidates for which we or they obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and continuing review by the FDA, Department of Justice, Department of Health and Human Services' Office of Inspector General, state attorneys general, members of Congress, and the public. When the FDA or comparable foreign regulatory authorities issue regulatory approval for a product candidate, the regulatory approval is limited to those specific uses and indications for which a product is approved. If we are not able to obtain FDA approval for any desired uses or indications for our products and product candidates, we may not market or promote our products for those indications and uses, referred to as off-label uses, and our business may be adversely affected. We further must be able to sufficiently substantiate any claims that we make for our products including claims comparing our products to other companies' products.

While physicians may choose to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those tested in clinical studies and approved by the regulatory authorities, we are prohibited from marketing and promoting the products for indications and uses that are not specifically approved by the FDA or comparable foreign regulatory authorities. These off-label uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. Regulatory authorities in the United States and in many other major markets do not generally restrict or regulate the behavior of physicians in their choice of treatment within the practice of medicine. Regulatory authorities do, however, restrict communications by pharmaceutical companies concerning off-label use.

If we are found to have impermissibly promoted any of our product candidates, we may become subject to significant liability and government fines. The FDA and other agencies actively enforce the laws and regulations regarding product promotion, particularly those prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted a product may be subject to significant sanctions. 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 of permanent injunctions under which specified promotional conduct is changed or curtailed. Thus, we and any of our collaborators will not be able to promote any products we develop for indications or uses for which they are not approved.

In the United States, engaging in the impermissible promotion of our products, following approval, for off-label uses can also subject us to false claims and other litigation under federal and state statutes, including fraud and abuse and consumer protection laws, which can lead to civil and criminal penalties and fines, agreements with governmental authorities that materially restrict the manner in which we promote or distribute drug products and do business through, for example, corporate integrity agreements, suspension or exclusion from participation in federal and state healthcare programs, and debarment from government contracts and refusal of future orders under existing contracts. Recent court decisions have impacted the FDA's enforcement activity regarding off-label promotion in light of First Amendment considerations; however, there are still significant risks in this area in part due to the potential False Claims Act exposure. The False Claims Act allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims, or causing others to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government decides to intervene and prevails in the qui tam lawsuit, the individual will share in the proceeds from any fines or settlement funds. If the government declines to intervene, the individual may pursue the case alone. Under the False Claims Act, a penalty may be imposed for each false claim, for example, a claim for payment for each prescription for the product, and, when aggregated, these penalties often total millions of dollars and incentivize qui tam lawsuits. These False Claims Act lawsuits against pharmaceutical companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements, up to $3.0 billion, pertaining to certain sales practices and promoting off-label drug uses. This growth in litigation has increased the risk that a pharmaceutical company will have to defend a false claim action; pay settlement fines or restitution, as well as criminal and civil penalties; agree to comply with burdensome reporting and compliance obligations; and be excluded from Medicare, Medicaid, or other federal and state healthcare programs. If we or our collaborators do not lawfully promote our approved products, if any, we may become subject to such litigation and, if we do not successfully defend against such actions, those actions may have a material adverse effect on our business, financial condition, results of operations, and prospects.

In the United States, the distribution of product samples to physicians must further comply with the requirements of the U.S. Prescription Drug Marketing Act. If the FDA determines that our promotional materials or activities violate its regulations and policies pertaining to product promotion, it could request that we modify our promotional materials or activities or subject us to regulatory or other enforcement actions, including issuance of warning letters or untitled letters, suspension or withdrawal of an approved product from the market, requests for recalls, payment of civil fines, disgorgement of money, imposition of operating restrictions, injunctions, or criminal prosecution. These regulatory and enforcement actions could significantly harm our business, financial condition, results of operations, and prospects.

We are, and if any of our product candidates receive regulatory approval, will continue to be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, any of our product candidates, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

Any product candidate for which we obtain marketing approval will be subject to extensive and ongoing requirements of and review by the FDA and other regulatory authorities, including requirements related to the manufacturing processes, post-approval clinical data, labeling, packaging, distribution, adverse event reporting, storage, recordkeeping, export, import, advertising, marketing, and promotional activities for such product. These requirements further include submissions of safety and other post-marketing information, including manufacturing deviations and reports; registration and listing requirements; the payment of annual program fees for our product candidates, if approved; continued compliance with cGMP requirements relating to manufacturing, quality control, quality assurance, and corresponding maintenance of records and documents; requirements regarding the distribution of samples to physicians and recordkeeping; and good clinical practices, or GCPs, for any clinical trials that we conduct post-approval. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses and populations for which the product may be marketed or to the conditions of approval, including significant safety warnings, including boxed warnings, contraindications, and precautions that are not desirable for successful commercialization and any requirement to implement a REMS that render the approved product not commercially viable or other post-market requirements or restrictions. Any such restrictions could limit sales of the product.

We and any of our collaborators, including our contract manufacturers, could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs. Application holders must further notify the FDA, and depending on the nature of the change, obtain FDA pre-approval for product and manufacturing changes. Application fees may apply to certain changes.

In addition, later discovery of previously unknown adverse events or that the drug is less effective than previously thought or other problems with our products, manufacturers, or manufacturing processes, or failure to comply with regulatory requirements both before and after approval, may yield various results, including:

- restrictions on manufacturing or distribution, or marketing of such products;
- restrictions on the labeling, including required additional warnings, such as black box warnings, contraindications, precautions, and restrictions on the approved indication or use;
- modifications to promotional pieces;
- requirements to conduct post-marketing studies or clinical trials;
- clinical holds or termination of clinical trials;
- requirements to establish or modify a REMS or a comparable foreign authority may require that we establish or modify a similar strategy, that may, for instance, require us to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients, or restrict distribution of the product, if and when approved, and impose burdensome implementation requirements on us;
- changes to the way the drug is administered;
- liability for harm caused to patients or subjects;
- reputational harm;

- the drug becoming less competitive;
- warning or untitled letters;
- suspension of marketing or withdrawal of the products from the market;
- regulatory authority issuance of safety alerts, Dear Healthcare Provider letters, press releases, or other communications containing warnings or other safety information about the drug;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, damages, restitution, or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure or detention;
- FDA debarment, debarment from government contracts, and refusal of future orders under existing contracts, exclusion from federal healthcare programs, consent decrees, or corporate integrity agreements; or
- injunctions or the imposition of civil or criminal penalties, including imprisonment.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, or could substantially increase the costs and expenses of commercializing such product, which in turn could delay or prevent us from generating significant revenues from its sale. Any of these events could further have other material and adverse effects on our operations and business and could adversely impact our stock price and could significantly harm our business, financial condition, results of operations, and prospects.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit, or delay regulatory approval of our product candidates or that could impose additional regulatory obligations on us if our product candidates are approved. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and be subject to regulatory enforcement action.

Should any of the above actions take place, they could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

If we obtain approval to commercialize our product candidates outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

If any of our product candidates are approved for commercialization, we may enter into agreements with third parties to market them on a worldwide basis or in more limited geographical regions. We expect that we will be subject to additional risks related to entering into international business relationships, including:

- different regulatory requirements for approval of drugs in foreign countries;

- the potential for so-called parallel importing, particularly within Europe, which is what happens when a local seller, faced with high or higher local prices, opts to import goods from a foreign market (with low or lower prices) rather than buying them locally with EU laws supporting such “free movement of goods” within the EU;

- stricter harmonized EU rules on data privacy particularly in relation to health data than is the case in the United States which are being further toughened with EU General Data Protection Regulation, or the GDPR, which became enforceable beginning May 25, 2018;

- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;

- unexpected changes in tariffs, trade barriers, and regulatory requirements and in the health care policies of foreign jurisdictions;

- economic weakness, including inflation, or political instability in particular foreign economies and markets;

- compliance with tax, employment, immigration, and labor laws for employees living or traveling abroad;

- foreign taxes, including withholding of payroll taxes;

- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;

- difficulties staffing and managing foreign operations;

- workforce uncertainty in countries where labor unrest is more common than in the United States and worker rights tend to be stronger;

- costs of compliance with U.S. laws and regulations for foreign operations, including the Foreign Corrupt Practices Act or comparable foreign regulations, and the risks and costs of noncompliance;

- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and

- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods, and fires.

These and other risks associated with our international operations may materially adversely affect our ability to attain or maintain profitable operations.

We will need to obtain FDA approval (and that of comparable foreign regulatory authorities) of any proposed product names, and any failure or delay associated with such approval may adversely affect our business.

Any name we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the U.S. Patent and Trademark Office, or USPTO. The FDA typically conducts a review of proposed product names, including an evaluation of the potential for confusion with other product names. The FDA may also object to a product name if it believes the name inappropriately implies medical claims or contributes to an overstatement of efficacy. If the FDA objects to any of our proposed product names, we may be required to adopt alternative names for our product candidates. If we adopt alternative names, we would lose the benefit of any existing trademark applications for such product candidate and may be required to expend significant additional resources in an effort to identify a suitable product name that would qualify under applicable trademark laws,

not infringe the existing rights of third parties, and be acceptable to the FDA. We may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product candidates.

RISKS RELATED TO THE COMMERCIALIZATION OF OUR PRODUCT CANDIDATES

We face significant competition from other pharmaceutical and biotechnology companies, academic institutions, government agencies, and other research organizations. Our operating results will suffer if we fail to compete effectively.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of pain and CNS disorders. Potential competitors also include academic institutions, government agencies, and other public and private research organizations that conduct research, seek patent protection, and establish collaborative arrangements for research, development, manufacturing, and commercialization.

Specifically, there are a large number of companies developing or marketing therapies for CNS disorders, including many major pharmaceutical and biotechnology companies. Among the companies that currently market or are developing therapies that, if approved, our product candidates would potentially compete with include: Acadia Pharmaceuticals, Inc.; Alder Biopharmaceuticals, Inc.; Alkermes plc; Allergan plc; Amgen Inc.; Biohaven Pharmaceutical Holding Company Ltd.; Carbylan Therapeutics, Inc.; Eli Lilly and Company; Flexion Therapeutics, Inc.; Grunenthal GmbH; Intra-Cellular Therapies, Inc.; Janssen Research & Development, LLC; Jazz Pharmaceuticals plc; Levolta Pharmaceuticals, Inc.; Otsuka Pharmaceutical Co. Ltd.; and OPKO Health, Inc.

Our commercial opportunities could be reduced or eliminated if our competitors develop and commercialize products that are safer, are 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. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products or therapeutically similar lower cost brands. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products, which would further impact our commercialization efforts.

Generic forms of the active ingredients of our product candidates, including zoledronic acid, DM, bupropion, meloxicam, rizatriptan, reboxetine, and esomeprazole, are available in the United States or abroad and could be used off-label. Any such off-label use could adversely affect our profitability and have a negative effect on our operating results and financial condition. For example, even though zoledronic acid is not currently approved for the treatment of pain, we would not be able to prevent a physician from prescribing zoledronic acid in intravenous form for such treatment. Nor could we prevent a payor from offering favorable coverage for such product and disadvantaging our product candidates, even if the generics would be used off-label.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with, or acquisition by large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel and establishing

clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If the FDA or comparable foreign regulatory authorities approve generic or similar versions of any of our products that receive marketing approval, or such authorities do not grant our products appropriate periods of data exclusivity before approving generic or similar versions of our products, the sales of our products could be adversely affected.

Once an NDA is approved, the covered product becomes a "reference listed drug" in the FDA's Orange Book. Manufacturers may seek approval of generic versions of reference listed drugs through submission of ANDAs in the United States. In support of an ANDA, a generic manufacturer need not conduct full clinical studies. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use or labeling, among other commonalities, as the reference listed drug and that the generic version is bioequivalent to the reference listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Recently, the FDA and Congress have also taken steps to encourage increased generic drug competition in the market. Generic products may be significantly less costly to bring to market than the reference listed drug and companies that produce generic products are generally able to offer them at lower prices, and are generally preferred by third-party payors. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed drug is typically lost to the generic product.

Moreover, in addition to generic competition, we could face competition from other companies seeking approval of drug products that are similar to ours using the 505(b)(2) pathway. Such applicants may be able to rely on our product candidates, if approved, or other approved drug products or published literature to develop drug products that are similar to ours. The introduction of a drug product similar to our product candidates could expose us to increased competition.

Further, if we do not file a patent infringement lawsuit against a generic manufacturer within 45 days of receiving notice of its paragraph IV certification, the ANDA or 505(b)(2) applicant would not be subject to a 30-month stay. Litigation or other proceedings to enforce or defend intellectual property rights are often very complex in nature, may be expensive and time consuming, may divert our management's attention from our core business, and may result in unfavorable results that could adversely impact our ability to prevent third parties from competing with our products. Accordingly, upon approval of our product candidates we may be subject to generic competition or competition from similar products, or may need to commence patent infringement proceedings, which would divert our resources.

We currently anticipate that we may be eligible for three years of non-patent marketing exclusivity in the United States for our product candidates if they are approved. These three years, however, would only protect our modifications in formulation or approved uses in comparison to the reference listed drug and would not prevent other companies from submitting full NDAs, and would not prevent physicians from prescribing other products off-label or third party payors from reimbursing for them. Moreover, a 505(b)(2) applicant could rely on a reference listed drug that is not one of our product candidates, or published literature, in which case any periods of patent or non-patent protection may not prevent FDA making an approval effective.

Competition that our products may face from generic or similar versions of our products could materially and adversely impact our future revenue, profitability, and cash flows and substantially limit our ability to obtain a return on the investments we have made in those product candidates.

AXS-12 and AXS-02 received Orphan Drug Designation from the FDA. However, there is no guarantee that we will receive this designation for any of our other product candidates, or receive or maintain any corresponding benefits for any of our other product candidates that may receive Orphan Drug Designation in the future, including periods of exclusivity.

AXS-12 received Orphan Drug Designation from the FDA for the treatment of narcolepsy. AXS-02 received Orphan Drug Designation from the FDA for the treatment of CRPS. We may also seek Orphan Drug Designation for our other product candidates, as appropriate.

Orphan Drug Designation, however, may be lost if the indications for which we develop any of our future product candidates do not meet the orphan drug criteria. Moreover, following product approval, orphan drug exclusivity may be lost if the FDA determines, among other reasons, that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition. Even if we obtain orphan drug exclusivity for any of our current or future product candidates, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. Even after an orphan product is approved, the FDA can subsequently approve a product containing the same principal molecular features for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer or more effective or makes a major contribution to patient care.

The FDA or the EMA may grant orphan exclusivity to two different sponsors for the same compound or active molecule and for the same indication. For example, subsequent to our Orphan Drug Designation, the FDA granted Orphan Drug Designation to Thar Pharmaceuticals, Inc. for a zoledronic acid-containing product for the treatment of CRPS. Thar Pharmaceuticals was subsequently acquired by Grunenthal GmbH. Although we are no longer pursuing CRPS, if Grunenthal GmbH or another sponsor had received FDA approval for a zoledronic acid-containing product for the treatment of CRPS before we had obtained FDA approval for AXS-02 for the treatment of pain associated with CRPS, we would have been prevented from launching our product in the United States for this indication for a period of at least 7 years. If another sponsor had received EMA approval for a zoledronic acid-containing product for the treatment of CRPS before we had obtained EMA approval for AXS-02 for the treatment of pain associated with CRPS, we would have been prevented from launching our product in the EU for this indication for a period of at least 10 to 12 years.

In response to a recent court decision regarding the plain meaning of the exclusivity provision of the Orphan Drug Act, the FDA may undertake a reevaluation of aspects of its orphan drug regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business, financial condition, results of operations, and prospects could be harmed.

If we are unable to establish effective marketing and sales capabilities or enter into agreements with third parties to market and sell our product candidates, if they are approved, we may be unable to generate product revenues.

We currently do not have a commercial infrastructure for the marketing, sale, and distribution of pharmaceutical products. If approved, in order to commercialize our products, we must build our marketing, sales, and distribution capabilities or make arrangements with third parties to perform these services. We may not be successful in doing so. If one of our product candidates is approved by the FDA, we plan to build a commercial infrastructure, including the creation of a specialty sales force to launch that product candidate throughout the United States. In the future, we may seek to further penetrate the U.S. market by expanding our sales force or through collaborations with other pharmaceutical or biotechnology companies or third-party manufacturing and sales organizations. If approved for marketing outside the United States, we intend to commercialize our product candidates outside the United States with a marketing and sales collaborator or collaborators, rather than with our own sales force.

We have no prior experience in the marketing, sale, and distribution of pharmaceutical products, and there are significant risks involved in the building and managing of a commercial infrastructure. The establishment and development of our own sales force and related compliance plans to market any products we may develop will be

expensive and time consuming and could delay any product launch, and we may not be able to successfully develop this capability. We, or our future collaborators, will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train, manage, and retain marketing and sales personnel. In the event we are unable to develop a marketing and sales infrastructure, we may not be able to commercialize any of our current or future product candidates, which would limit our ability to generate product revenues. Factors that may inhibit our efforts to commercialize any of our current or future product candidates on our own include:

- our inability to recruit, train, manage, and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any of our current or future product candidates;
- our inability to effectively oversee a geographically dispersed sales and marketing team;
- the costs associated with training sales and marketing personnel on legal and regulatory compliance matters and monitoring their actions;
- an inability to secure adequate coverage and reimbursement by government and private health plans;
- the clinical indications and labeled claims for which the product is approved;
- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling;
- any distribution and use restrictions imposed by the FDA or to which we agree as part of a mandatory REMS or voluntary risk management plan;
- liability for sales or marketing personnel who fail to comply with the applicable legal and regulatory requirements;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization or engaging a contract sales organization.

Although our current plan is to hire most of our sales and marketing personnel only if a product candidate is approved by the FDA, we will incur expenses prior to product launch in recruiting this sales force and developing a marketing and sales infrastructure. If a commercial launch is delayed as a result of FDA requirements or other reasons, we would incur these expenses prior to being able to realize any revenue from sales of our product candidates. Even if we are able to effectively hire a sales force and develop a marketing and sales infrastructure, our sales force and marketing teams may not be successful in commercializing any of our current or future product candidates.

In the event we are unable to collaborate with a third-party marketing and sales organization to commercialize any approved product candidates outside the United States, our ability to generate product revenues may be limited. To the extent we rely on third parties to commercialize any products for which we obtain regulatory approval, we may receive less revenues than if we commercialized these products ourselves. In addition, we would have less control over the sales efforts of any other third parties involved in our commercialization efforts, and could be held liable if they failed to comply with applicable legal or regulatory requirements.

If any of our current or future product candidates do not achieve broad market acceptance, the revenues that we generate from their sales will be limited.

We have never commercialized a product candidate for any indication. Even if any of our current or future product candidates are approved by the appropriate regulatory authorities for marketing and sale, it may not gain acceptance among physicians, patients, third-party payors, and others in the medical community. If any product candidates for which we obtain regulatory approval do not gain an adequate level of market acceptance, we may not generate significant product revenues or become profitable. Market acceptance of any of our current or future product candidates by the medical community, patients, and third-party payors will depend on a number of factors, some of which are beyond our control. For example, physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies. Even if physicians prescribe our products, third party payors may not consider them cost effective without a significant price concession, which could negatively impact our revenue.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of any of our product candidates will depend on a number of factors, including:

- the efficacy of our product candidates;
- the prevalence and severity of adverse events associated with such product candidate;
- the clinical indications for which the product is approved and the approved claims that we may make for the product;
- limitations or warnings contained in the product's FDA-approved labeling, including potential limitations or warnings for such product candidate, that may be more restrictive than other competitive products;
- changes in the standard of care for the targeted indications for such product candidate, which could reduce the marketing impact of any claims that we could make following FDA approval, if obtained;
- the relative convenience and ease of administration of such product candidate;
- cost of treatment versus economic and clinical benefit in relation to alternative treatments or therapies;
- the availability of adequate coverage or reimbursement by third parties, such as insurance companies and other healthcare payors, and by government healthcare programs, including Medicare and Medicaid;
- the willingness of third party payors to prefer similar but less expensive products even if not approved for our product's indication;
- the extent and strength of our marketing and distribution of such product candidate;
- the safety, efficacy, and other potential advantages over, and availability of, alternative treatments already used or that may later be approved for any of our intended indications;
- distribution and use restrictions imposed by the FDA with respect to such product candidate or to which we agree as part of a mandatory risk evaluation and mitigation strategy or voluntary risk management plan;

- the timing of market introduction of such product candidate, as well as competitive products;
- our ability to offer such product candidate for sale at competitive prices, including prices that are competitive with generic products;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the clinical indications for which such product candidate is approved;
- the extent and strength of our third-party manufacturer and supplier support;
- the approval of other new products for the same indications;
- adverse publicity about the product or favorable publicity about competitive products; and
- potential product liability claims.

Our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful. Even if the medical community accepts that one of our product candidates is safe and effective for its approved indications, physicians and patients may not immediately be receptive to such product candidate and may be slow to adopt it as an accepted treatment of the approved indication. It is unlikely that any labeling approved by the FDA will contain claims that one of our product candidates is safer or more effective than competitive products or will permit us to promote such product candidate as being superior to competing products. Further, the availability of inexpensive generic forms of pain management products for acute pain may also limit acceptance of certain of our product candidates among physicians, patients, and third-party payors. If any of our current or future product candidates is approved but does not achieve an adequate level of acceptance among physicians, patients, and third-party payors, we may not generate meaningful revenues from our product candidates, and we may not become profitable.

The ability of patients to purchase certain of the active ingredients of our product candidates in generic form could put us at a competitive disadvantage. For example, in some foreign jurisdictions, generic oral forms of DM and bupropion are currently available individually for consumer purchase. In addition, physicians may prescribe generic zoledronic acid for the treatment of pain off-label. Any use of these generic forms of the active molecules of our product candidates could adversely affect our business and our results of operations.

The potential market opportunities for our product candidates are difficult to precisely estimate. Our estimates of the potential market opportunities are predicated on many assumptions including industry knowledge and publications, third-party research reports, and other surveys. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management and are inherently uncertain, and the reasonableness of these assumptions has not been assessed by an independent source. If any of the assumptions proves to be inaccurate, the actual markets for our product candidates could be smaller than our estimates of the potential market opportunities.

We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability for any of our current or future product candidates and may have to limit their commercialization.

The use of any of our current or future product candidates in clinical trials, and the sale of any of our product candidates for which we obtain regulatory approval, exposes us to the risk of product liability claims. We face inherent risk of product liability related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any product candidates that we may develop. For example, we may be sued if any product candidate we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing,

manufacturing, marketing, or sale. 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, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. Product liability claims might be brought against us by consumers, healthcare providers, or others using, administering, or selling our products. If we cannot successfully defend ourselves against these claims, we will incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of merit or eventual outcome, liability claims may result in:

- loss of revenue from decreased demand for our products and/or product candidates;
- impairment of our business reputation or financial stability;
- costs of related litigation;
- substantial monetary awards to patients or other claimants;
- diversion of management attention;
- loss of revenues;
- withdrawal of clinical trial participants and potential termination of clinical trial sites or entire clinical programs;
- the inability to commercialize our product candidates;
- significant negative media attention;
- decrease in our stock price;
- initiation of investigations and enforcement actions by regulators; and
- product recalls, withdrawals, or labeling, marketing, or promotional restrictions.

We have obtained limited product liability insurance coverage for our products and our clinical trials with a $8 million annual aggregate coverage limit. We have also obtained local policies in those foreign jurisdictions where it was appropriate. However, our insurance coverage may not reimburse us or may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, 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 due to liability. We intend to expand our insurance coverage to include the sale of commercial products if we obtain FDA approval for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing, or at all. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business and our prospects.

RISKS RELATED TO OUR DEPENDENCE ON THIRD PARTIES

We rely, and expect to continue to rely, on third parties to conduct, supervise, and monitor our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials or failing to comply with regulatory requirements.

We rely on third-party CROs to conduct, supervise, and monitor our preclinical studies and certain clinical trials for our product candidates and do not currently plan to independently conduct preclinical studies or clinical trials of any other potential product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions, and clinical investigators, to conduct our preclinical studies and clinical trials. While we have agreements governing their activities, we have limited influence over their actual performance and control only certain aspects of their activities. The failure of these third parties to successfully carry out their contractual duties or meet expected deadlines could substantially harm our business because we may not obtain marketing approval for or commercialize our product candidates in a timely manner or at all. Moreover, these agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that would delay our product development activities and adversely affect our business.

Our reliance on these third parties for development activities will reduce our control over these activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our preclinical trials are conducted in accordance with good laboratory practice, or GLP, as appropriate. Moreover, the FDA and comparable foreign regulatory authorities require us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial participants are protected. As a clinical trial sponsor, we also have regulatory requirements that directly apply to us. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical investigators, and trial sites. If we or any of our CROs fail to comply with applicable GCPs, we or our CROs may be subject to enforcement or other legal actions, 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.

In addition, once we have an approved product, we will be required to report certain financial interests of our third-party investigators if these relationships exceed certain financial thresholds or meet other criteria. The FDA and comparable foreign regulatory authorities may question the integrity of the data from those clinical trials conducted by investigators who previously served or currently serve as scientific advisors or consultants to us from time to time and receive cash compensation in connection with such services or otherwise receive compensation from us that could be deemed to impact study outcome, proprietary interests in a product candidate, certain company equity interests, or significant payments of other sorts.

We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product candidates that were produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register certain clinical trials and post the results of certain completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in enforcement actions and adverse publicity.

Our CROs may also have relationships with other entities, some of which may be our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, non-clinical, and preclinical programs. If these third parties do not successfully carry out their contractual duties, meet expected

deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed, or terminated and we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates, or we or they may be subject to regulatory enforcement actions. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. To the extent we are unable to successfully identify and manage the performance of third-party service providers in the future, our business may be materially and adversely affected.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays could occur, which could compromise our ability to meet our desired development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects, and results of operations.

If the manufacturers upon whom we rely fail to produce our product candidates in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues.

We do not manufacture any of our product candidates, and we do not currently plan to develop any capacity to do so. We currently outsource all manufacturing of our product candidates to third parties typically without any guarantee that there will be sufficient supplies to fulfill our requirements or that we may obtain such supplies on acceptable terms. Any delays in obtaining adequate supplies with respect to our product candidates may delay the development or commercialization of our product candidates. Moreover, we do not yet have agreements established regarding commercial supply of our product candidates, and we may not be able to establish or maintain commercial manufacturing arrangements on commercially reasonable terms for any of our current or future product candidates for which we obtain approval in the future.

We may not succeed in our efforts to establish manufacturing relationships or other alternative arrangements for any of our existing or future product candidates and programs. Our product candidates may compete with other products and product candidates for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that are both capable of manufacturing for us and willing to do so. If our existing third-party manufacturers, or the third parties that we engage in the future to manufacture a product for commercial sale or for our clinical trials, should cease to continue to do so for any reason, we likely would experience delays in obtaining sufficient quantities of our product candidates for us to meet commercial demand or to advance our clinical trials while we identify and qualify replacement suppliers. If for any reason we are unable to obtain adequate supplies of our product candidates or the drug substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively. Further, even if we do establish such collaborations or arrangements, our third-party manufacturers may breach, terminate, or not renew these agreements.

Any problems or delays we experience in preparing for commercial-scale manufacturing of a product candidate may result in a delay in FDA approval of the product candidate or may impair our ability to manufacture commercial quantities or such quantities at an acceptable cost, which could result in the delay, prevention, or impairment of clinical development and commercialization of our product candidates and could adversely affect our business. For example, our manufacturers will need to produce specific batches of our product candidates to demonstrate acceptable stability under various conditions and for commercially viable lengths of time. We and our contract manufacturers will need to demonstrate to the FDA and other regulatory authorities that this is acceptable stability data for our product candidates, as well as validate methods and manufacturing processes, in order to receive regulatory approval to commercialize any

of our current or future product candidates. Furthermore, if our commercial manufacturers fail to deliver the required commercial quantities of bulk drug substance or finished product on a timely basis and at commercially reasonable prices, we would likely be unable to meet demand for our products and we would lose potential revenues.

We have a limited number of contract manufacturers for our products. At times we may have only one manufacturer for a product. In addition, we do not have any long-term commitments from our suppliers of clinical trial material or guaranteed prices for our product candidates. The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production. These problems include difficulties with production costs and yields; quality control, including stability of the product candidate and quality assurance testing; shortages of qualified personnel; and compliance with strictly enforced federal, state, and foreign regulations. Our manufacturers may not perform as agreed. If our manufacturers were to encounter any of these difficulties, our ability to provide product candidates to patients in our clinical trials and for commercial use, if approved, would be jeopardized.

In addition, all manufacturers of our product candidates must comply with cGMP requirements enforced by the FDA and comparable foreign regulatory authorities that are applicable to both finished drug products and active pharmaceutical ingredients used both for clinical and commercial supply, through its facilities inspection program. Our manufacturers must be approved by the FDA and comparable foreign regulatory authorities pursuant to inspections that will be conducted after we submit our marketing applications to the agency and comparable foreign regulatory authorities. The cGMP requirements include quality control, quality assurance, and the maintenance of records and documentation. Manufacturers of our product candidates may be unable to comply with our specifications, these cGMP requirements and with other FDA, state, and foreign regulatory requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure or maintain regulatory approval for their manufacturing facilities. While we are ultimately responsible for the manufacture of our product candidates, other than through our contractual arrangements, we have little control over our manufacturers' compliance with these regulations and standards. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for, or market our product candidates, if approved. A failure to comply with these requirements may result in regulatory enforcement actions against our manufacturers or us, including fines and civil and criminal penalties, including imprisonment; suspension or restrictions of production; suspension, delay, or denial of product approval or supplements to approved products; clinical holds or termination of clinical studies; warning or untitled letters; regulatory authority communications warning the public about safety issues with the drug; refusal to permit the import or export of the products; product seizure, detention, or recall; suits under the civil False Claims Act; corporate integrity agreements; consent decrees; or withdrawal of product approval. If the safety of any quantities supplied is compromised due to our manufacturers' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our product candidates.

Any failure or refusal to supply our product candidates or components for our current or future product candidates that we may develop could delay, prevent, or impair our clinical development or commercialization efforts. Any change in our manufacturers could be costly because the commercial terms of any new arrangement could be less favorable and because the expenses relating to the transfer of necessary technology and processes could be significant.

We may rely on third parties to perform many essential services for any products that we commercialize, including services related to warehousing and inventory control, distribution, government price reporting, customer service, accounts receivable management, cash collection, and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize any of our current or future product candidates will be significantly impacted and we may be subject to regulatory sanctions.

We may retain third-party service providers to perform a variety of functions related to the sale and distribution of any of our current or future product candidates, key aspects of which will be out of our direct control. These service providers may provide key services related to warehousing and inventory control, distribution, government price reporting, customer service, accounts receivable management, and cash collection, and, as a result, most of our inventory may be stored at a single warehouse maintained by one such service provider. If we retain a service provider, we would substantially rely on it as well as other third-party providers that perform services for us, including entrusting our inventories of products to their care and handling. If these third-party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, or otherwise do not carry out their contractual duties to us, or encounter physical or natural damage at their facilities, our ability to deliver product to meet commercial demand would be significantly impaired and we may be subject to regulatory enforcement action.

In addition, we may engage third parties to perform various other services for us relating to adverse event reporting, safety database management, fulfillment of requests for medical information regarding our product candidates and related services. If the quality or accuracy of the data maintained by these service providers is insufficient, or these third parties otherwise fail to comply with regulatory requirements related to adverse event reporting, we could be subject to regulatory sanctions.

Additionally, if a third party errs in calculating government pricing information from transactional data in our financial records, it could impact our discount and rebate liability and potentially cause government programs to overpay providers for our products.

Any collaboration arrangements that we are a party to or may enter into in the future may not be successful, which could adversely affect our ability to develop and commercialize our product candidates.

Our business model is to commercialize our product candidates in the United States and generally to seek future collaboration arrangements with pharmaceutical or biotechnology companies, or academic institutions, for the development or commercialization of our product candidates in the rest of the world. For example, in December 2017 we entered into a research collaboration agreement with Duke University for the conduct of a Phase 2 clinical trial of AXS-05 for smoking cessation treatment. We currently have not entered into any sub-license agreements. Our current and future collaboration arrangements may not be successful, and the success of them will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaboration arrangements. For clinical trials of our product candidates being conducted by our collaborators, for example the Phase 2 clinical trial of AXS-05 for smoking cessation in collaboration with Duke University, we rely on timeline estimates provided by our collaborators for these trials. Such timeline estimates may differ materially from actual trial completion dates. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision making authority.

We may license the right to market and sell our product candidates under our collaborators' labeler codes. Alternatively, we may enter into agreements with collaborators to market and sell our product candidates under our own labeler code, in which case errors and omissions by collaborators in capturing and transmitting transactional data may impact the accuracy of our government price reporting.

Collaborations with pharmaceutical companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation. Any future collaborations we might enter into may pose a number of risks, including the following:

- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;
- collaborators could fail to make timely regulatory submissions for a product candidate;
- collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product candidate or product;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation, or the preferred course of development, might cause delays or termination of the research, development, or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation; and
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability.

If any collaborations we might enter into in the future do not result in the successful development and commercialization of products or if one of our collaborators subsequently terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under the agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates and our product platform.

Additionally, if any future collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our reputation in the business and financial communities could be adversely affected.

We may in the future determine to collaborate with additional pharmaceutical and biotechnology companies and academic institutions for the development and potential commercialization of any of our current or future product candidates. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for collaboration will depend upon, among other things, 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. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms, or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform and our business may be materially and adversely affected.

We are dependent on third parties to decide to utilize our product candidates to make them readily available at the point of care throughout their networks of pharmacies.

In addition to extensive internal efforts, the successful commercialization of our product candidates will require many third parties, over whom we have no control, to decide to utilize our product candidates, and to make them readily available at the point of care throughout their networks of pharmacies. These third parties include HMOs, long term care facilities, and pharmacy benefit managers, or PBMs, which use pharmacy and therapeutics committees, commonly referred to as P&T committees, to make purchasing and reimbursement decisions. Generally, before an HMO or long-term care facility will acquire any of our product candidate for its own pharmacies, or a PBM will pay retail network pharmacies on behalf of its health plans, any such product candidates must be approved for addition to that organization's list of approved drugs, or formulary list, by the organization's P&T committee. An institutional P&T committee typically governs all matters pertaining to the use of medications within the institution, including review of medication formulary data and recommendations for the appropriate use of drugs within the institution to the medical staff. PBM P&T committees develop the criteria for plan beneficiaries to access prescription medication, including such cost control measures as step therapy and prior authorization. The frequency of P&T committee meetings varies considerably, and P&T committees often require additional information to aid in their decision-making process, so we may experience substantial delays in obtaining formulary approvals. Additionally, P&T committees may be concerned that the cost of acquiring any of our product candidates for use in their institutions or reimbursing retail pharmacies outweighs clinical benefits and will resist efforts to add any such product candidate to the formulary, or implement restrictions on the usage of the drug in order to control costs. Third party payors often have tiered formularies in which the non-preferred drugs have significantly higher co-pays, causing prescription rejections, and define therapeutic class broadly to increase competition for preferred status. We cannot guarantee that we will be successful in getting the approvals we need from enough P&T committees quickly enough to maintain and grow sales of any of our product candidates.

We are dependent upon our license agreements with an entity owned by our Chief Executive Officer and Chairman of the Board related to the development of our current product candidates, and if the agreements are terminated for any reason our business will be materially harmed.

In 2012, we entered into three exclusive license agreements with Antecip Bioventures II LLC, or Antecip, an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which we were granted exclusive licenses to develop, manufacture, and commercialize Antecip's patents and applications related to the

development of AXS-02 and AXS-05, as well as AXS-04, a product candidate that is currently in early stage development, anywhere in the world for veterinary and human therapeutic and diagnostic use. The agreements were amended in August 2015 to update the schedule of patents and applications subject to the license agreements. Pursuant to the agreements, we are required to use commercially reasonable efforts to develop, obtain regulatory approval for, and commercialize AXS-02, AXS-05, and AXS-04. Under the terms of the agreements, we are required to pay to Antecip a royalty equal to 4.5% for AXS-02, 3.0% for AXS-05, and 1.5% for AXS-04, of net sales of products containing the licensed technology by us, our affiliates, or permitted sublicensees. These royalty payments are subject to reduction by an amount up to 50.0% of any required payments to third parties. Unless earlier terminated by a party for cause or by us for convenience, the agreements remain in effect on a product-by-product and country-by-country basis until the later to occur of (1) the applicable product is no longer covered by a valid claim in that country or (2) 10 years from the first commercial sale of the applicable product in that country. Upon expiration of the agreements with respect to a product in a country, our license grant for that product in that country will become a fully paid-up, royalty-free, perpetual non-exclusive license. If Antecip terminates any of the agreements for cause, or if we exercise our right to terminate any of the agreements for convenience, the rights granted to us under such terminated agreement will revert to Antecip. To date, we have not been required to make any payments to Antecip under any of the license agreements. If any of the license agreements with Antecip are terminated for any reason, our business, financial condition, results of operations, and prospects will be materially harmed.

RISKS RELATED TO INTELLECTUAL PROPERTY

It is difficult and costly to protect our proprietary rights and as a result we may not be able to ensure their protection. In addition, patents have a limited lifespan and will eventually expire.

Market exclusivity awarded by the FDA upon the approval of an NDA is limited in scope and duration. Our commercial success will depend in part on obtaining, maintaining, enforcing, and defending against third-party challenges, our patent and trade secret protection for any of our current and future product candidates that we may develop, license, or acquire, and the related manufacturing methods. We will only be able to fully protect our technologies from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them.

The patent prosecution process is expensive and time consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, should we enter into additional collaborations we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance, and enforcement of our patents. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in pharmaceutical or biotechnology patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. Moreover, the patent application process is also subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting any of our current or future product candidates that we may develop, license, or acquire by obtaining and defending patents. For example:

- we may not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
- we may not have been the first to file patent applications for these inventions;

- others may independently develop similar or alternative technologies or duplicate any of our product candidates or technologies;
- it is possible that none of the pending patent applications will result in issued patents;
- the issued patents may not cover commercially viable active products, may not provide us with any competitive advantages, or may be successfully challenged by third parties;
- we may not develop additional proprietary technologies that are patentable;
- patents of others may have an adverse effect on our business;
- noncompliance with governmental patent agencies requirements 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, potentially allowing competitors to enter the market earlier than would otherwise have been the case;
- our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with, or eliminate our ability to make, use, and sell our potential product candidates; or
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of available patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns.

Patents have a limited lifespan. In most countries, including the United States, the expiration of a patent is typically 20 years from the date that the application for the patent is filed. Various extensions of patent term may be available in particular countries; however, in all circumstances the life of a patent, and the protection it affords, has a limited term. If we encounter delays in obtaining regulatory approvals, the period of time during which we could market a product under patent protection could be reduced. We expect to seek extensions of patent terms where these are available in any countries where we are prosecuting patents. Such possible extensions include those permitted under the Drug Price Competition and Patent Term Restoration Act of 1984 in the United States, which permits a patent term extension of up to five years to cover an FDA-approved product. The actual length of the extension will depend on the amount of patent term lost while the product was in clinical trials. However, the applicable authorities, including the USPTO and the FDA in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data, and then may be able to launch their product earlier than might otherwise be the case.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith 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. In particular, under the Leahy-Smith Act, the United States transitioned in March 2013 to a "first to file" system in which the first inventor to file a patent application will be entitled to the patent. Third parties are allowed to submit prior art before the issuance of a patent by the USPTO, and may become involved in post-grant proceedings including reexamination, post-grant review, inter-partes review, or derivation or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position.

The USPTO has developed regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, did not become effective until March 16, 2013. However, the full impact of the Leahy-Smith Act and the courts' review of any appeals to related proceedings, is in its early stages. Accordingly, the full impact that the Leahy-Smith Act will have on the operation of our business is not clear. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, as well as our ability to bring about timely favorable resolution of any disputes involving our patents and the patents of others. Patent applications in the United States are maintained in confidence for at least 18 months after their earliest effective filing date. Consequently, we cannot be certain we were the first to invent or the first to file patent applications on our current or future product candidates that we may develop, license, or acquire. In the event that a third party has also filed a U.S. patent application relating to our product candidates or a similar invention, we may have to participate in interference proceedings declared by the USPTO to determine priority of invention in the United States. The costs of these proceedings could be substantial and it is possible that our efforts would be unsuccessful, resulting in a material adverse effect on our U.S. patent position. The results of these types of proceedings may reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop, or commercialize current or future product candidates. Such results could have a material adverse effect on our business, financial condition, results of operations, and prospects.

In addition, the patentability of claims in pending patent applications covering AXS-02, AXS-05, or any other of our current or future product candidates can be challenged by third parties during prosecution in the USPTO, for example by third-party observations and derivation proceedings, and the validity of claims in issued patents can be challenged by third parties in various post-grant proceedings such as post-grant review, reexamination, and inter-partes review proceedings. For example, in December 2016, a petition for post-grant review of U.S. Patent No. 9,283,239, which we refer to as the ‘239 patent, was filed at the USPTO by Grunenthal GmbH, or Grunenthal, and the post-grant review was instituted on July 7, 2017. In addition, in May 2017, a petition for post-grant review of U.S. Patent No. 9,408,862, which we refer to as the ‘862 patent, was filed at the USPTO by Grunenthal; in October 2017, a petition for post-grant review of U.S. Patent No. 9,539,268, which we refer to as the ‘268 patent, was filed at the USPTO by Grunenthal; in April 2018, a petition for post-grant review of U.S. Patent No. 9,707,245, which we refer to as the ‘245 patent, was filed at the USPTO by Grunenthal; in August 2018, a petition for post-grant review of U.S. Patent No. 9,820,999, which we refer to as the ‘999 patent, was filed at the USPTO by Grunenthal; in October 2018, a petition for post-grant review of U.S. Patent No. 9,867,839, which we refer to as the ‘839 patent, and on January 3, 2018, petitions for post-grant reviews of U.S. Patents No. 9,931,352, which we refer to as the ‘352 patent, 10,039,774, which refer to as the ‘774 patent, and 10,052,338, which we refer to as the ‘338 patent, were filed at the USPTO by Grunenthal.

The ‘239 patent contains claims directed to the use of orally administered zoledronic acid, the active moiety in AXS-02, for the treatment of CRPS, and is one of several issued patents containing claims covering the use of AXS-02 for the treatment of CRPS. The ‘862 and ‘268 patents contain claims directed to certain dosage forms containing zoledronic acid, the active moiety in AXS-02. The ‘862 patent also contains claims directed to certain oral dosage forms containing zoledronic acid, including AXS-02, and use of certain oral dosage forms containing zoledronic acid, including AXS-02, for the treatment of knee pain and arthritis, respectively. The ‘862 and ‘268 patents are two of several issued patents containing claims covering dosage forms of zoledronic acid such as AXS-02, and the use of certain oral dosage forms containing zoledronic acid, including AXS-02, in the treatment of knee pain and arthritis. The ‘245, ‘999, ‘352, ‘774, and ‘338 patents contain claims directed to the use of neridronic acid for the treatment of CRPS, and is one of several issued patents containing claims covering the use of neridronic acid for the treatment of CRPS. The ‘839 patent contains claims directed to the use of neridronic acid and oral zoledronic acid for the treatment of joint pain. The petitions request that the Patent Trial and Appeal Board, or PTAB, initiate proceedings to review the validity of the ‘239, the ‘862, the ‘268, the ‘245, the ‘999, the ‘839, the ‘352, the ‘774, and the ‘338 patents.

In April 2017, we responded to and opposed Grunenthal's petition for post-grant review of the ‘239 patent. In July 2017, the PTAB issued a decision in which it refused to institute a post-grant-review of the ‘239 patent on the grounds of novelty, obviousness, or enablement. The PTAB ruled that Grunenthal had not established that it is more likely than not that the stated prior art would have rendered the claims of the ‘239 patent obvious or not novel, and that Grunenthal had failed to demonstrate that it is more likely than not that the claims are unpatentable for lack of enablement. However, a post-grant review was instituted on the ground of written description. The PTAB further ordered that the post-grant review for the ‘239 patent be limited to written description and that no other grounds of unpatentability are authorized for post-grant review. In October 2017, we responded to the PTAB decision to institute a post-grant review. On June 22, 2018, the Patent Trial and Appeal Board, or PTAB, entered a final written decision holding that the claims were invalid for lack of written description.

In August 2017, we responded to and opposed the petition for the ‘862 patent. In November 2017, the PTAB rendered a decision to initiate a post-grant review for that patent. In February 2018, we responded to the PTAB decision to institute a post-grant review. On November 14, 2018, the Patent Trial and Appeal Board, or PTAB, entered a final written decision holding that the claims were invalid for lack of enablement, and for some claims, lack of novelty and/or obviousness. On January 16, 2019, we appealed the decision of the PTAB to the United States Court of Appeals for the Federal Circuit.

In February 2018, we responded to and opposed the petition for the ‘268 patent. In May 2018, the PTAB rendered a decision to initiate a post-grant review for the patent. In August 2018, we responded to the PTAB decision to institute a post-grant review.

In October 2018, the PTAB rendered a decision to initiate a post grant review for the ‘245 patent. In July, 2019, we responded to the PTAB decision to institute a post-grant review.

In February 2019, the PTAB rendered a decision to initiate a post-grant review for the ‘999 patent.

Any patent claim the PTAB determines to be unpatentable as a result of these proceedings would be stricken from the challenged patents or modified. Additionally, we cannot be sure that the validity of the claims in other issued patents covering any of our current or future product candidates will not also be challenged, or that Grunenthal will not file any additional petitions for post-grant review with respect to any of our current or future product candidates. We may incur increased expenses related to the growth of our intellectual property portfolio and to its defense.

Furthermore, we may not have identified all United States and foreign patents or published applications that affect our business either by blocking our ability to commercialize our drugs or by covering similar technologies that affect our drug market. In addition, some countries, including many in Europe, do not grant patent claims directed to methods of treating humans, and in these countries patent protection may not be available at all to protect our product candidates. Even if patents issue, we cannot guarantee that the claims of those patents will be valid and enforceable or provide us with any significant protection against competitive products, or otherwise be commercially valuable to us.

We also rely on trade secrets to protect our technology, particularly where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. While we use reasonable efforts to protect our trade secrets, our licensors, employees, consultants, contractors, outside scientific collaborators, and other advisors may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third party illegally obtained and is using our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods, and know how.

Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, 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 USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment, and other similar provisions during the patent prosecution process. Periodic maintenance fees, renewal fees, annuity fees, and various other governmental fees on patents or patent applications will be due to be paid to the USPTO and various patent agencies outside of the United States in several stages over the lifetime of the patents and applications. We have systems in place to remind us to pay these fees, and we employ and rely on reputable law firms and other professionals to effect payment of these fees to the USPTO and non-U.S. patent agencies for the patents and patent applications we own and those that we in-license. We also employ reputable law firms and other professionals to help us comply with the various documentary and other procedural requirements with respect to the patents and patent applications that we own and those that we in-license. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

If we or any future collaboration partner are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in any litigation would harm our business.

Our ability to develop, manufacture, market, and sell any of our current and future product candidates depends upon our ability to avoid infringing the proprietary rights of third parties, and our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market, and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the general field of treatment and management of pain and other CNS disorders and cover the use of numerous compounds and formulations in our targeted markets. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. Because of the uncertainty inherent in any patent or other litigation involving proprietary rights, we and our licensors may not be successful in defending intellectual property claims by third parties, which could have a material adverse effect on our business, financial condition, results of operations, and prospects. Regardless of the outcome of any litigation, defending the litigation may be expensive, time consuming, and distracting to management. In addition, because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that any of our current or future product candidates may infringe. There could also be existing patents of which we are not aware that any of our current or future product candidates may inadvertently infringe.

If a third party claims that we infringe on their products or technology, we could face a number of issues, including:

- infringement and other intellectual property claims which, whether meritorious or not, can be expensive and time consuming to litigate and can divert management's attention from our core business;
- substantial damages for past infringement which we may have to pay if a court decides that our product infringes on a competitor's patent;
- a court prohibiting us from selling or licensing our product unless the patent holder licenses the patent to us, which it would not be required to do;
- if a license is available from a patent holder, we may have to pay substantial royalties or grant cross licenses to our patents; and

- redesigning our product candidates and processes so they do not infringe, which may not be possible or could require substantial funds and time.

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms, or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations, and prospects.

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.

Competitors may infringe our issued patents, our in-licensed patents, or other intellectual property that we own or in-license. Under the terms of our license agreements with Antecip, if we believe a third party is infringing on the patents subject to the licenses, we are obligated, at our own expense, to initiate suit against those third parties. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part; construe the patent's claims narrowly; or 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 proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. 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.

Most of our competitors are larger than we are and have substantially greater resources than we do. They are, therefore, likely to be able to sustain the costs of complex patent litigation longer than we could. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs, in-license needed technology, or enter into development partnerships that would help us bring our product candidates to market.

We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property, including patent rights that are important or necessary to the development or commercialization of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties. Such a license may not be available on commercially reasonable terms, or at all, which could materially harm our business, financial condition, results of operations, and prospects.

We may be subject to claims that our employees, independent contractors, or consultants have wrongfully used or disclosed alleged trade secrets of their former employers or other third parties.

As is common in the biotechnology and pharmaceutical industry, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these individuals or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers.

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.

We may be unable to adequately prevent disclosure of trade secrets and other proprietary information.

We rely on trade secrets to protect our proprietary technological advances and know-how, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, contractors, outside scientific collaborators, sponsored researchers, and other advisors, including the third parties we rely on to manufacture our product candidates, to protect our trade secrets and other proprietary information. However, any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets. Accordingly, these agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights. In addition, others may independently discover our trade secrets and proprietary information. Further, the FDA, as part of its Transparency Initiative, a proposal to increase disclosure and make data more accessible to the public, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all. Failure to obtain or maintain trade secret protection could enable competitors to use our proprietary information to develop products that compete with our products or cause additional, material adverse effects upon our competitive business position and financial results.

We or our licensors may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting, and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. 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 United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement rights are not as strong as those in the United States. These products may compete with our product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents generally. 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 and 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 or our licensors' intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

RISKS RELATED TO LEGAL AND COMPLIANCE MATTERS

If we fail to comply with federal state, and foreign healthcare laws, including fraud and abuse and health and other information privacy and security laws, we could face substantial penalties and our business, financial condition, results of operations, and prospects could be adversely affected.

As a pharmaceutical company, we are subject to many federal and state healthcare laws, including those described in the "Business—Government Regulation and Product Approval" section of this Annual Report on Form 10-K, such as the federal Anti-Kickback Statute, the federal civil and criminal False Claims Act, the civil monetary penalties statute, the Medicaid Drug Rebate statute and other price reporting requirements, the Veterans Health Care Act of 1992, the federal Health Insurance Portability and Accountability Act of 1996 (as amended by the Health Information Technology for Economics and Clinical Health Act), the Foreign Corrupt Practices Act of 1977, the Patient Protection and Affordable Care Act of 2010, and similar state and foreign laws. Even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid, or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We would be subject to healthcare fraud and abuse by both the federal government and the states in which we conduct our business.

If we or our operations are found to be in violation of any federal or state healthcare law, or any other governmental regulations that apply to us, we may be subject to penalties, including civil, criminal, and administrative penalties, damages, fines, disgorgement, debarment from government contracts, refusal of orders under existing contracts, exclusion from participation in U.S. federal or state health care programs, corporate integrity agreements, and the curtailment or restructuring of our operations, any of which could materially adversely affect our ability to operate our business and our financial results. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including our collaborators, is found not to be in compliance with applicable laws, it may be subject to criminal, civil, or administrative sanctions, including but not limited to, exclusions from participation in government healthcare programs, which could also materially affect our business.

Although an effective compliance program can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Moreover, achieving and sustaining compliance with applicable federal and state fraud laws may prove costly. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

If the government or third-party payors fail to provide adequate coverage and payment rates for any of our current or future product candidates, or if HMOs or long-term care facilities choose to use therapies that are less expensive, our revenue and prospects for profitability will be limited.

In both domestic and foreign markets, sales of our future products will depend in part upon the availability of coverage and reimbursement from third-party payors. Such third-party payors include government health programs such as Medicare and Medicaid, managed care providers, private health insurers, and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. If reimbursement is not available, or is available only to limited levels, our product candidates may be competitively disadvantaged, and we, or our collaborators, 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, or our collaborators, to establish or maintain a market share sufficient to realize a sufficient return on our or their investments. Alternatively, securing favorable reimbursement terms may require us to compromise pricing and prevent us from realizing an adequate margin over cost.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing, and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted.

In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of our collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval. Our ability, and the ability of our collaborators, to commercialize our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers, and other organizations. Regulatory authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Several third-party payors are requiring that drug companies provide them with predetermined discounts from list prices, are using preferred drug lists to leverage greater discounts in competitive classes, are disregarding therapeutic differentiators within classes, and are challenging the prices charged for drugs. Brand drugs without generic equivalents are often included in therapeutic classes with other brands that have generic versions and may be similarly disadvantaged by the availability of low cost alternatives within the class, particularly if a generic version of the same agent is available in another form.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. Third-party coverage and reimbursement for our products or product candidates for which we receive regulatory approval may not be available or adequate in either the United States or international markets, which could have a negative effect on our business, financial condition, results of operations, and prospects.

Assuming coverage is approved, the resulting reimbursement payment rates might not be adequate. If payors subject our product candidates to maximum payment amounts, or impose limitations that make it difficult to obtain reimbursement, providers may choose to use therapies which are less expensive when compared to our product candidates. Additionally, if payors require high copayments, beneficiaries may decline prescriptions and seek alternative therapies. We may need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to the satisfaction of hospitals and other target customers and their third-party payors. Such studies might require us to commit a significant amount of management time and financial and other resources. Our future products might not ultimately be considered cost-effective. Adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

In addition, federal programs impose penalties on manufacturers of drugs marketed under an NDA, including 505(b)(2) drugs, in the form of mandatory additional rebates and/or discounts if commercial prices increase at a rate greater than the Consumer Price Index-Urban, and these rebates and/or discounts, which can be substantial, may impact our ability to raise commercial prices. Regulatory authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of our collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or those of our collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us, or our collaborators, to decrease, discount, or rebate a portion of the price we, or they, might establish for products, which could result in lower than anticipated product revenues. If the realized prices for our products, if any, decrease or if governmental and other third-party payors do not provide adequate coverage or reimbursement, our prospects for revenue and profitability will suffer.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale, and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may only be temporary. Reimbursement rates may vary, by way of example, according to the use of the drug and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

Prices paid for a drug also vary depending on the class of trade. Prices charged to government customers are subject to price controls, including ceilings, and private institutions obtain discounts through group purchasing organizations. Net prices for drugs may be further reduced by mandatory discounts or rebates required by government healthcare programs and demanded by private payors. Drugs approved under NDAs, including 505(b)(2) drugs, are subject to greater discounts and reporting obligations under federal programs than drugs approved under ANDAs, and the inflation penalty applicable to these products can equal the selling price. It is also not uncommon for market conditions to warrant multiple discounts to different customers on the same unit, such as purchase discounts to institutional care providers and rebates to the health plans that pay them, which reduces the net realization on the original sale.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. We, and our collaborators, cannot be sure that coverage will be available for any product candidate that we, or they, commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any our product candidates for which we obtain marketing approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

We are subject to new legislation, regulatory proposals, and healthcare payor initiatives that may increase our costs of compliance, and adversely affect our ability to market our products, obtain collaborators, and raise capital.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities, and affect our ability, or the ability of our collaborators, to profitably sell any products for which we obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or our collaborators, may receive for any approved products.

For example, legislative changes have been proposed and adopted since enactment of the Affordable Care Act, or ACA, in 2010. These changes include, among other things, aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which became effective on April 1, 2013, and significant reductions to Medicare payment to certain safety net hospitals for outpatient drugs purchased under the “340B” drug discount program, effective January 1, 2018. These laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our drugs, if approved, and, accordingly, on our results of operations.

On January 20, 2017, the current administration 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 or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Further, in December 2017, the current administration signed into law legislation that repealed the individual mandate in the ACA and increased manufacturer liability for payment on behalf of Medicare Part D beneficiaries during the coverage gap. Congress also could consider

additional legislation to repeal and replace elements of the ACA. The United States District Court for the Northern District of Texas struck down the ACA, deeming it unconstitutional given that Congress repealed the individual mandate in 2017. While this decision has been stayed pending outcome of an appeal to the Fifth Circuit Court of Appeals, so the ruling does not have immediate effect, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the ACA will impact the ACA. It is also unclear how regulatory and subregulatory policy, which fluctuate continually, may affect interpretation and implementation of the ACA and its practical effects on our business.

While the full effect that the ACA may have on our business continues to evolve, we expect that the ACA, as well as other federal and state healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria, increased regulatory burdens and operating costs, decreased net revenue from our pharmaceutical products, decreased potential returns from our development efforts, and additional downward pressure on the price that we receive for any approved drug. There is increasing focus on the price of drugs, and states such as California have begun enacting transparency laws aimed at curbing drug price increases. Any reduction in reimbursement from Medicare or other government healthcare programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs.

Legislative and regulatory proposals may also be made to expand post-approval requirements and restrict sales and promotional activities for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance, or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

In addition, there have been a number of other legislative and regulatory proposals aimed at changing the pharmaceutical industry. For instance, the enacted Drug Supply Chain Security Act, or DSCSA imposes obligations on manufacturers of prescription drug products for commercial distribution, regulating the distribution of the products at the federal level, and sets certain standards for federal or state registration and compliance of entities in the supply chain (manufacturers and repackagers, wholesale distributors, third-party logistics providers, and dispensers). The DSCSA preempts previously enacted state pedigree laws and the pedigree requirements of the Prescription Drug Marketing Act, or PDMA. Trading partners within the drug supply chain must now ensure certain product tracing requirements are met that they are doing business with other authorized trading partners; and they are required to exchange transaction information, transaction history, and transaction statements. Further, the DSCSA limits the distribution of prescription pharmaceutical products and imposes requirements to ensure overall accountability and security in the drug supply chain. As of November 27, 2018 product identifier information (an aspect of the product tracing scheme) is required.

Compliance with the federal track and trace requirements may increase our operational expenses and impose significant administrative burdens. As a result of these and other new proposals, we may determine to change our current manner of operation, provide additional benefits, or change our contract arrangements, any of which could have a material adverse effect on our business, financial condition, and results of operations.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In international markets, reimbursement and health care payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. There can be no assurance that our products will be considered cost-effective by third-party payors, that an adequate level of reimbursement will be available, or that the third-party payors' reimbursement policies will not adversely affect our

ability to sell our products profitably. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Our employees, independent contractors, consultants, commercial partners, principal investigators, or CROs may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees, independent contractors, consultants, commercial partners, principal investigators, or CROs could include intentional, reckless, negligent, or unintentional failures to comply with FDA regulations, comply with applicable fraud and abuse laws, provide accurate information to the FDA, report financial information or data accurately, or disclose unauthorized activities to us. This misconduct could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter this type of misconduct, and the precautions we take to detect and prevent this activity may not be effective 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 be in compliance with such 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, financial condition, and results of operations, including the imposition of significant fines or other sanctions.

Our third-party manufacturers may use hazardous materials in the production of our product candidates and if so, they must comply with environmental laws and regulations, which can be expensive and restrict how we or they do business.

Manufacturing activities for the production of our product candidates involve the controlled storage, use, and disposal of hazardous materials, including the components of our product candidates, and other hazardous compounds. Our third-party manufacturers and we are subject to federal, state, and local laws and regulations governing the use, manufacture, storage, handling, release, and disposal of, and exposure to, these hazardous materials. Violation of these laws and regulations could lead to substantial fines and penalties. Although we believe that our safety procedures, and those of our third-party manufacturers, for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state or federal authorities may curtail our use of these materials and interrupt our business operations. In addition, we could become subject to potentially material liabilities relating to the investigation and cleanup of any contamination, whether currently unknown or caused by future releases.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous, or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health, and safety laws and regulations. These current or future laws and regulations may impair our research, development, or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties, or other sanctions.

RISKS RELATED TO OUR BUSINESS OPERATIONS

We will need to significantly increase the size of our organization, and we may experience difficulties in managing growth.

As of March 11, 2019, we had only 29 full-time employees. We will need to substantially expand our managerial, commercial, financial, manufacturing, and other personnel resources in order to manage our operations and

prepare for the commercialization of our product candidates, if approved. Our management, personnel, systems, and facilities currently in place may not be adequate to support this future growth. In addition, we may not be able to recruit and retain qualified personnel in the future, particularly for sales and marketing positions, due to competition for personnel among pharmaceutical businesses, and the failure to do so could have a significant negative impact on our future product revenues and business results. Our need to effectively manage our operations, growth and various projects requires that we:

- continue the hiring and training of personnel for an effective commercial organization in anticipation of the potential approval of our product candidates, and establish appropriate systems, policies and infrastructure to support that organization;
- ensure that our consultants and other service providers successfully carry out their contractual obligations, provide high quality results, and meet expected deadlines;
- continue to carry out our own contractual obligations to our licensors and other third parties; and
- continue to improve our operational, financial, and management controls, reporting systems, and procedures.

We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our development and commercialization goals.

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

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 assure you that, following any such acquisition, we will achieve the expected synergies to justify the transaction.

We may not be able to manage our business effectively if we are unable to attract and retain key personnel.

We may not be able to attract or retain qualified management and commercial, scientific, and clinical personnel due to the intense competition for qualified personnel among biotechnology, pharmaceutical, and other businesses. If we are not able to attract and retain necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the skills and leadership of our management team, including Dr. Herriot Tabuteau, our Chief Executive Officer and Chairman of the Board. We do not have formal employment agreements with any of our management team. However, we typically enter into offer letters with our executive officers and key personnel. Our senior management may terminate their employment with us at any time. If we lose one or more members of our senior management team, our ability to successfully implement our business strategy could be seriously harmed. Replacing these employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of, and commercialize products successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain, or motivate additional key personnel. We do not maintain “key person” insurance for any of our executives or other employees.

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

As a public company, we continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC, and the Nasdaq Global Market, impose various requirements on public companies, including requiring establishment and maintenance of effective disclosure controls and internal control over financial reporting and changes in corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and have made some activities more time-consuming and costly.

Section 404(a) of the Sarbanes-Oxley Act requires annual management assessments of the effectiveness of our internal control over financial reporting. However, for as long as we remain an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act, we intend to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not "emerging growth companies" including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act. We may take advantage of these reporting exemptions until we are no longer an "emerging growth company." We will remain an "emerging growth company" until the earliest of (i) the last day of the fiscal year in which we have total annual gross revenues of $1.07 billion or more; (ii) December 31, 2020; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a "large accelerated filer" under the rules of the SEC.

Our testing, or the subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses. We will incur substantial accounting expense and expend significant management efforts to comply with internal control over financial reporting requirements. We currently do not have an internal audit group, and we may need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge. Moreover, if we are not able to comply with these requirements in a timely manner or if we or our independent registered public accounting firm identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline, and we could be subject to sanctions or investigations by the Nasdaq Global Market, the SEC or other regulatory authorities, which would require additional financial and management resources.

If we fail to maintain an effective system of internal control over financial reporting in the future, we may not be able to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common stock.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation, could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act, or the subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness or significant deficiency in our internal control over financial reporting once that firm begins its Section 404 reviews, we could lose investor confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by the Nasdaq Global Market, the SEC or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Our business and operations would suffer in the event of system failures.

Despite our implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war, telecommunication and electrical failures, cyber-attacks or cyber-intrusions over the Internet, attachments to emails, persons inside our organization, or persons with access to systems inside our organization. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our product candidate development programs. For example, the loss of clinical trial data from completed, ongoing, or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of personal, confidential, or proprietary information, we could incur liability and the further development of any of our product candidates could be delayed.

Our failure to comply with international data protection laws and regulations could lead to government enforcement actions and significant penalties against us, and adversely impact our operating results.

EU member states and other foreign jurisdictions, including Switzerland, have adopted data protection laws and regulations which impose significant compliance obligations. Moreover, the collection and use of personal health data in the EU, which was formerly governed by the provisions of the EU Data Protection Directive, was replaced with the EU General Data Protection Regulation, or the GDPR, in May 2018. The GDPR, which is wide-ranging in scope, imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, the security and confidentiality of the personal data, data breach notification and the use of third party processors in connection with the processing of personal data. The GDPR also imposes strict rules on the transfer of personal data out of the EU to the U.S., provides an enforcement authority and imposes large penalties for noncompliance, including the potential for fines of up to €20 million or 4% of the annual global revenues of the noncompliant company, whichever is greater. The GDPR requirements apply not only to third-party transactions, but also to transfers of information between us and our subsidiaries, including employee information. The recent implementation of the GDPR has increased our responsibility and liability in relation to personal data that we process, including in clinical trials, and we may in the future be required to put in place additional mechanisms to ensure compliance with the GDPR, which could divert management’s attention and increase our cost of doing business. In addition, new regulation or legislative actions regarding data privacy and security (together with applicable industry standards) may increase our costs of doing business. In this regard, we expect that there will continue to be new proposed

laws, regulations and industry standards relating to privacy and data protection in the United States, the EU and other jurisdictions, and we cannot determine the impact such future laws, regulations and standards may have on our business.

Our failure to comply with state and/or national data protection laws and regulations could lead to government enforcement actions and significant penalties against us, and adversely impact our operating results.

There are numerous other laws and legislative and regulatory initiatives at the federal and state levels addressing privacy and security concerns, and some state privacy laws apply more broadly than the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations. For example, California recently enacted legislation – the California Consumer Privacy Act, or CCPA – which goes into effect January 1, 2020. The CCPA, among other things, creates new data privacy obligations for covered companies and provides new privacy rights to California residents, including the right to opt out of certain disclosures of their information. The CCPA also creates a private right of action with statutory damages for certain data breaches, thereby potentially increasing risks associated with a data breach. Legislators have stated that they intend to propose amendments to the CCPA before it goes into effect, and the California Attorney General will issue clarifying regulations. Although the law includes limited exceptions, including for certain information collected as part of clinical trials as specified in the law, it may regulate or impact our processing of personal information depending on the context. It remains unclear what, if any, modifications will be made to this legislation or how it will be interpreted.

RISKS RELATED TO OWNERSHIP OF OUR COMMON STOCK

An active trading market for our common stock may not be sustained.

In November 2015, we closed our initial public offering. Prior to our initial public offering, there was no public market for shares of our common stock. Although we have completed our initial public offering and shares of our common stock are listed and trading on The Nasdaq Global Market, an active trading market for our shares may not be sustained. If an active market for our common stock does not continue, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or sell their shares at or above the prices at which they acquired their shares or sell their shares at the time they would like to sell. Any inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares.

The market price of our common stock may be highly volatile.

The trading price of our common stock is likely to be volatile. As a result of this volatility, investors may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

- delays in the commencement, enrollment, and ultimate completion, of our planned and ongoing Phase 3 clinical trials for our product candidates;
- any delay or refusal on the part of the FDA in approving an NDA for any of our current and future product candidates;
- the commercial success of any of our current and future product candidates, if approved by the FDA;
- results of clinical trials of any of our current and future product candidates or those of our competitors;
- actual or anticipated variations in quarterly or annual operating results;
- failure to meet or exceed financial projections we provide to the public, if any;

- failure to meet or exceed the estimates and projections of the investment community, including securities analysts;
- introduction of competitive products or technologies;
- changes or developments in laws or regulations applicable to our product candidates;
- the perception of the pharmaceutical industry by the public, legislatures, regulators, and the investment community;
- general economic and market conditions and overall fluctuations in U.S. equity markets;
- data or security breaches;
- developments concerning our sources of manufacturing supply, warehousing, and inventory control;
- disputes or other developments relating to patents or other proprietary rights;
- additions or departures of key scientific or management personnel;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- capital commitments;
- investors' general perception of our company and our business;
- announcements and expectations of additional financing efforts, including the issuance of debt, equity or convertible securities;
- sales of our common stock, including sales by our directors and officers or significant stockholders;
- changes in the market valuations of companies similar to us;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, or divestitures;
- general conditions or trends in our industry; and
- the other factors described in this "Risk Factors" section.

In addition, the stock market in general, and the market for small pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

Further, in the past, stockholders have initiated class action lawsuits against pharmaceutical and biotechnology companies following periods of volatility in the market prices of these companies' stocks. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management's attention and resources from our business.

If equity research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business, or our market, our stock price and trading volume could decline.

The trading market for our common stock is influenced by the research and reports that equity research analysts publish about us and our business. We do not have any control over the equity research analysts that provide research coverage of our common stock or the content and opinions included in their reports. The price of our stock could decline if one or more equity research analysts downgrades our stock or issue other unfavorable commentary or research. If one or more equity research analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- whether the FDA requires us to complete additional, unanticipated studies, tests, or other activities prior to approving any of our current and future product candidates, which would likely further delay any such approval;
- if any of our current or future product candidates is approved, our ability to establish the necessary commercial infrastructure to launch this product candidate without substantial delays, including hiring sales and marketing personnel and contracting with third parties for warehousing, distribution, cash collection, and related commercial activities;
- our ability to identify and enter into third-party manufacturing arrangements capable of manufacturing any of our current or future product candidates in commercial quantities;
- our execution of other collaborative, licensing, or similar arrangements and the timing of payments we may make or receive under these arrangements;
- variations in the level of expenses related to our future development programs;
- any product liability or intellectual property infringement lawsuit in which we may become involved;
- regulatory developments affecting our current and future product candidates, or the product candidates of our competitors; and
- if any of our current or future product candidates receive regulatory approval, the level of underlying demand for such product candidate and wholesaler buying patterns.

If our quarterly or annual operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly or annual fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

Raising additional funds by issuing securities may cause dilution to existing stockholders and raising funds through lending and licensing arrangements may restrict our operations or require us to relinquish proprietary rights.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, grants, and license and development agreements in connection with any collaborations. We do not have any committed external source of funds. To the extent that we raise additional capital by issuing equity securities, our existing stockholders' ownership will be diluted, and the terms of

these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity 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.

If we raise additional funds through collaborations, strategic alliances, or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs, or product candidates or grant licenses on terms that may not be favorable to us. Any debt financing we enter into may involve covenants that restrict our operations. These restrictive covenants may include limitations on additional borrowing and specific restrictions on the use of our assets as well as prohibitions on our ability to create liens, pay dividends, redeem our stock, or make investments. If we are unable to raise additional funds through equity or debt financings 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 product candidates that we would otherwise prefer to develop and market ourselves.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

As of March 11, 2019, our executive officers, directors, and 5% stockholders and their affiliates beneficially owned an aggregate of approximately 31% of our outstanding common stock. As a result, these stockholders have significant influence and may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This concentration of ownership could delay or prevent any acquisition of our company on terms that other stockholders may desire, and may adversely affect the market price of our common stock.

Some of these persons or entities may have interests different than yours. For example, these stockholders, if they acted together, could significantly influence all matters requiring approval by our stockholders, including the election of directors and the approval of mergers or other business combination transactions. These stockholders may be able to determine all matters requiring stockholder approval. The interests of these stockholders may not always coincide with our interests or the interests of other stockholders. This may also prevent or discourage unsolicited acquisition proposals or offers for our common stock that other stockholders may feel are in their best interest and our large stockholders may act in a manner that advances their best interests and not necessarily those of other stockholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock.

Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could cause our stock price to fall.

Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise adequate capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

As of March 11, 2019, we have outstanding 33,280,355 shares of common stock and 2,488,533 shares of common stock equivalents that would increase the number of common stock outstanding if these instruments were exercised or converted, including stock options to purchase common stock based on vesting requirements and warrants to purchase common stock. Of our currently outstanding shares of common stock, 25,199,214 are freely tradable. The remainder of the outstanding shares of common stock are held by our affiliates and may be considered “control securities” for purposes of Rule 144 under the Securities Act.

In addition, we have filed one or more registration statements on Form S-8 registering the issuance of an aggregate of 6,277,562 shares of common stock subject to options or other equity awards issued or reserved for future issuance under our 2015 Omnibus Incentive Compensation Plan, or the Plan. Shares registered under registration statements on Form S-8 will be available for sale in the public market subject to vesting arrangements and exercise of options, the lock-up agreements described above and the restrictions of Rule 144 in the case of our affiliates.

Our management will have broad discretion in the use of the net proceeds from our capital raises, including our December 2017 registered direct offering, our October 2018 registered direct offering, and the proceeds from sales pursuant to our previous Sales Agreement, and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from our capital raises, which we refer to as our Capital Raises, including our December 2017 registered direct offering, our October 2018 registered direct offering, and the proceeds from sales pursuant to our October 2017 "at-the-market" sales agreement with Leerink Partners LLC, which provided for the sale of up to $30.0 million of our common stock from time to time, and which was fully completed in January 2019, and our stockholders will not have the opportunity as part of their investment decision to assess whether the net proceeds from our Capital Raises are being used appropriately. You may not agree with our decisions, and our use of the proceeds may not yield any return on your investment. Because of the number and variability of factors that will determine our use of the net proceeds from our Capital Raisestheir ultimate use may vary substantially from their currently intended use. Our failure to apply the net proceeds of our Capital Raises effectively could compromise our ability to pursue our growth strategy and we might not be able to yield a significant return, if any, on our investment of those net proceeds. You will not have the opportunity to influence our decisions on how to use our net proceeds from our Capital Raises. Pending their use, we may invest the net proceeds from our Capital Raises in short-term, investment-grade, interest-bearing instruments and U.S. government securities. These temporary investments are not likely to yield a significant return.

We are an "emerging growth company" and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act, and we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We may take advantage of these reporting exemptions until we are no longer an emerging growth company. We cannot predict if investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

We will remain an emerging growth company until the earlier of (1) December 31, 2020, (2) the last day of the fiscal year (a) in which we have total annual gross revenue of at least $1.07 billion, or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (3) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. To the extent we are no longer eligible to use exemptions from various reporting requirements under the JOBS Act, we may be unable to realize our anticipated cost savings from these exemptions, which could have a material adverse impact on our operating results.

The use of our net operating loss carryforwards and research tax credits may be limited.

Our net operating loss carryforwards and any future research and development tax credits may expire and not be used. As of December 31, 2018, we had U.S. federal net operating loss, NOL, carryforwards of approximately $87 million. Net operating loss carry forwards amounting to $60 million generated before the 2018 tax year will start

expiring beginning 2033, if we have not used them prior to that time, and the net operating losses of approximately $27 million generated in 2018 has an indefinite carryforward period. Net operating loss carry forwards arising in taxable years ending after December 31, 2018 are no longer subject to expiration under the Internal Revenue Code of 1986, as amended, or the Code. Additionally, our ability to use any net operating loss and credit carryforwards to offset taxable income or tax, respectively, in the future will be limited under Sections 382 and 383 of the Code, respectively, if we have a cumulative change in ownership of more than 50% within a three-year period. The completion of our initial public offering, together with our March 2017 public offering, our December 2017 registered direct offering, our October 2018 registered direct offering, private placements and other transactions that have occurred, may trigger, or may have already triggered, such an ownership change. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo further ownership changes in the future. We have never completed an analysis as to whether such a change of ownership has occurred, but in such an event, we will be limited regarding the amount of net operating loss carryforwards and research tax credits that could be utilized annually in the future to offset taxable income or tax, respectively. Any such annual limitation may significantly reduce the utilization of the net operating loss carryforwards and research tax credits before they expire. In addition, certain states have suspended use of net operating loss carryforwards for certain taxable years, and other states are considering similar measures. As a result, we may incur higher state income tax expense in the future. Depending on our future tax position, continued suspension of our ability to use net operating loss carryforwards in states in which we are subject to income tax could have an adverse impact on our results of operations and financial condition.

Because we do not intend to pay dividends on our common stock, your returns will be limited to any increase in the value of our stock.

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business and do not anticipate declaring or paying any cash dividends on our common stock for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock, if any. Investors seeking cash dividends should not purchase our common stock.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result.

There are provisions in our amended and restated certificate of incorporation and amended and restated bylaws that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by you and other stockholders. For example, our board of directors will have the authority to issue up to 10,000,000 shares of preferred stock and to fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders.

In addition, we are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, or DGCL, which regulates corporate acquisitions by prohibiting Delaware corporations from engaging in specified business combinations with particular stockholders of those companies. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Our amended and restated certificate of incorporation designates the state or federal courts located in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that, subject to limited exceptions, the state and federal courts located in the State of Delaware will be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (3) any action asserting a claim against us arising pursuant to any provision of the DGCL, our amended and restated certificate of incorporation or our amended and restated bylaws, or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage such lawsuits against us and our directors, officers, and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 2. PROPERTIES.

Our corporate and executive office is located at 25 Broadway in New York, New York. We currently have a month-to-month agreement for office space that automatically renews for successive monthly periods, unless we provide notice of non-renewal. We believe that our current facilities are suitable and adequate to meet our current needs.

ITEM 3. LEGAL PROCEEDINGS.

We, and our subsidiaries, are not a party to, and our property is not the subject of, any material pending legal proceedings; however, we may become involved in various claims and legal actions arising in the ordinary course of business.

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

Part II

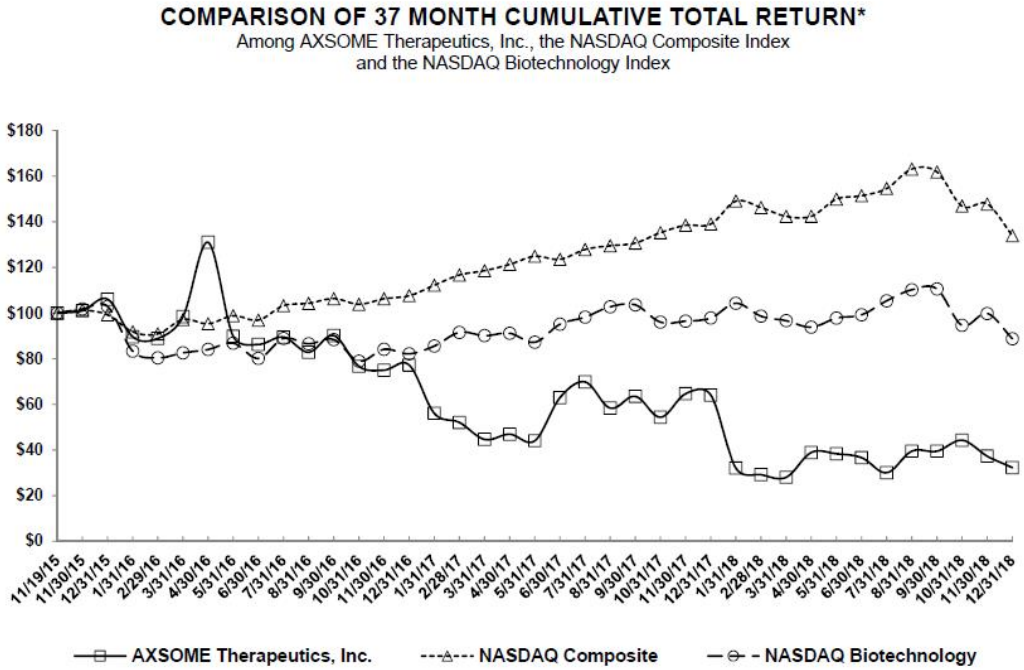
ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

Market Information

Our common stock has been listed on the Nasdaq Global Market since March 3, 2017 under the symbol "AXSM". Prior to that, our common stock was listed on the Nasdaq Capital Market since November 19, 2015, under the symbol "AXSM.". Prior to our initial public offering, there was no public market for our common stock.

Common Stock Performance Graph

The following graph illustrates a comparison of the total cumulative stockholder return for our common stock from November 19, 2015, which is the date our common stock first began trading on the Nasdaq Capital Market, through December 31, 2018 to two indices: the NASDAQ Composite Index and the NASDAQ Biotechnology Index. The graph assumes an initial investment of $100 on November 19, 2015, in our common stock, the NASDAQ Composite Index, and the NASDAQ Biotechnology Index and assumes reinvestment of dividends. The stockholder return shown in the graph below is not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns.



*$100 invested on 11/19/15 in stock or 10/31/15 in index, including reinvestment of dividends.
Fiscal year ending December 31.

Holders

The number of record holders of our common stock as of March 11, 2019 was 26. This number does not reflect the beneficial holders of our common stock who hold shares in street name through brokerage accounts or other nominees.

Dividends

We have never declared or paid any cash dividends on our common stock and do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be at the discretion of our board of directors, subject to applicable laws, and will depend on a number of factors, including our financial condition, results of operations, capital requirements, contractual restrictions, general business conditions, and any other factors that our board may deem relevant. In addition, the terms of our existing credit facility with Silicon Valley Bank, or SVB, and WestRiver Innovation Lending Fund VIII, L.P., or WestRiver, preclude us from paying cash dividends without SVB's and WestRiver's consent.

ITEM 6. SELECTED FINANCIAL DATA.

The following Statement of Operations Data for the years ended December 31, 2018, 2017 and 2016 and Balance Sheet Data as of December 31, 2018, 2017, and 2016, as set forth below are derived from our audited consolidated financial statements included elsewhere in this Annual Report on Form 10-K. This financial data should be read in conjunction with "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Item 8. Financial Statements and Supplementary Data." Our historical results are not necessarily indicative of the results that may be expected in the future.

	Year ended December 31,		
	2018	2017	2016
Statements of operations data:			
Operating expenses:			
Research and development	$ 23,495,055	$ 19,957,616	$ 21,199,860
General and administrative	9,351,522	7,206,691	6,343,648
Total operating expenses	32,846,577	27,164,307	27,543,508
Loss from operations	(32,846,577)	(27,164,307)	(27,543,508)
Interest and amortization of debt discount expense	(1,127,305)	(1,340,199)	(132,424)
Tax credit	217,418	207,114	474,279
Change in fair value of warrant liability	2,791,000	(646,000)	—
Net loss	$ (30,965,464)	$ (28,943,392)	$ (27,201,653)
Weighted average common shares outstanding—basic and diluted	26,883,656	22,764,606	19,150,690
Net loss per common share—basic and diluted	$ (1.15)	$ (1.27)	$ (1.42)

	As of December 31,		
	2018	2017	2016
Balance sheet data:			
Cash	$ 13,968,742	$ 34,021,123	$ 36,618,497
Total assets	15,379,279	35,555,564	38,212,608
Total current liabilities	10,821,938	12,175,336	7,170,712
Loan payable, long-term, net of discounts	3,619,420	6,663,005	9,470,445
Accumulated deficit	(107,550,307)	(76,584,843)	(47,641,451)
Total stockholders' equity	$ 937,921	$ 16,717,223	$ 21,571,451

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis contains forward-looking statements about our plans and expectations of what may happen in the future. You should read the following discussion and analysis in conjunction with "Item 6. Selected Financial Data," "Item 8. Financial Statements and Supplementary Data," and our consolidated financial statements beginning on page F-1 of this report. Forward-looking statements are based on a number of assumptions and estimates that are inherently subject to significant risks and uncertainties, and our results could differ materially from the results anticipated by our forward-looking statements as a result of many known or unknown factors, including, but not limited to, those factors discussed in "Item 1A. Risk Factors." See also the "Special Cautionary Notice Regarding Forward-Looking Statements" set forth at the beginning of this report.

Overview

We are a clinical-stage biopharmaceutical company developing novel therapies for the management of central nervous system, or CNS, disorders for which there are limited treatment options. By focusing on this therapeutic area, we are addressing significant and growing markets where current treatment options are limited or inadequate. Our core CNS portfolio includes four CNS product candidates, AXS-05, AXS-07, AXS-09, and AXS-12, which are being developed for multiple indications. The Axsome Pain and Primary Care business unit, or Axsome PPC, houses Axsome's pain and primary care assets, including AXS-02 and AXS-06, and intellectual property which covers these and related product candidates and molecules being developed by Axsome and others. We are conducting a Phase 3 trial with AXS-05 in treatment resistant depression, or TRD, which we refer to as the STRIDE-1 study, and a Phase 2/3 trial in agitation associated with Alzheimer's disease, or AD, which we refer to as the ADVANCE-1 study. We have completed a Phase 2 trial in major depressive disorder, or MDD, which we refer to as the ASCEND study. Additionally, AXS-05 is currently in a Phase 2 trial in smoking cessation. AXS-07 is being developed for the acute treatment of migraine. AXS-12 is being developed for the treatment of narcolepsy. We are also conducting a Phase 3 trial with AXS-02 in knee osteoarthritis, or OA, associated with bone marrow lesions, or BMLs, pursuant to a Special Protocol Assessment, or SPA, which we refer to as the COAST-1 study. AXS-06 is being developed for the treatment of osteoarthritis and rheumatoid arthritis and for the reduction of the risk of nonsteroidal anti-inflammatory drug, or NSAID, associated gastrointestinal ulcers. Additionally, we are currently evaluating other product candidates, which we intend to develop for CNS disorders. We aim to become a fully integrated biopharmaceutical company that develops and commercializes differentiated therapies that expand the treatment options available to caregivers and improve the lives of patients living with CNS disorders.

AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity under development for the treatment of CNS disorders. AXS-05 consists of bupropion and dextromethorphan, or DM, and utilizes Axsome's metabolic inhibition technology. We are developing AXS-05 initially for the following four indications: TRD, agitation associated with AD, MDD, and as an aid to smoking cessation. The DM component of AXS-05 is a non-competitive N-methyl-D-aspartate, or NMDA, receptor antagonist, also known as a glutamate receptor modulator. The DM component of AXS-05 is also a sigma-1 receptor agonist, nicotinic acetylcholine receptor antagonist, and inhibitor of the serotonin and norepinephrine transporters. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. We intend to seek U.S. Food and Drug Administration, or FDA, approval for AXS-05 utilizing the 505(b)(2) regulatory development pathway.

AXS-07, is a novel, oral, investigational medicine consisting of MoSEIC™, or Molecular Solubility Enhanced Inclusion Complex, meloxicam and rizatriptan. We are developing AXS-07 initially for the acute treatment of migraine. Meloxicam is a long-acting nonsteroidal anti-inflammatory drug, or NSAID, with COX-2, an enzyme involved in inflammation and pain pathways, preferential inhibition and potent pain-relieving effects. However standard meloxicam has an extended time to maximum plasma concentration, or T_{max}, which delays its onset of action. AXS-07 utilizes our proprietary MoSEIC™ technology to substantially increase the solubility and speed the absorption of meloxicam while potentially maintaining durability of action. Meloxicam is a new molecular entity for migraine enabled by our MoSEIC™ technology. Rizatriptan is a 5-$HT_{1B/D}$ agonist that inhibits calcitonin gene-related peptide-, or CGRP-mediated vasodilation, has been shown to have central trigeminal antinociceptive activity, and may reduce the release of inflammatory mediators from trigeminal nerves. Rizatriptan is approved as a single agent for the acute treatment of migraine. We intend to seek FDA approval for AXS-07 utilizing the 505(b)(2) regulatory development pathway.

AXS-09 is a novel, oral, investigational medicine consisting of esbupropion and DM, which is being developed for the treatment of CNS disorders. AXS-09 contains esbupropion, the chirally pure *S*-enantiomer of bupropion, as compared to the company's first generation product candidate AXS-05 which contains racemic bupropion, equal amounts of the *S*- and *R*-enantiomers. We have demonstrated in a Phase 1 trial that DM plasma levels are substantially increased into a potentially therapeutic range with repeated administration of AXS-09. Results of this Phase 1 trial coupled with preclinical data also indicate the potential for enhanced absorption and therapeutic effect of the *S*-enantiomer as compared to the *R*-enantiomer.

AXS-12, reboxetine, is a novel, oral, investigational medicine in development for treatment of narcolepsy. AXS-12 is a highly selective and potent norepinephrine reuptake inhibitor. The potential utility of AXS-12 in narcolepsy is supported by positive pre-clinical and preliminary clinical results in narcolepsy, and an extensive positive clinical safety record. Reboxetine, the active agent in AXS-12, significantly and dose-dependently reduced narcoleptic episodes in hypocretin-, or orexin-deficient mice, a well-established genetic animal model of narcolepsy.

The Axsome Pain and Primary Care business unit, or Axsome PPC, houses Axsome's pain and primary care assets, including AXS-02 and AXS-06, and intellectual property which covers these and related product candidates and molecules being developed by Axsome and others. AXS-02 is being developed for the treatment of knee osteoarthritis, or OA, associated with bone marrow lesions, or BMLs, and chronic low back pain, or CLBP, associated with Modic changes, or MCs. Lastly, AXS-06 is being developed for the treatment of osteoarthritis and rheumatoid arthritis and for the reduction of the risk of NSAID-associated gastrointestinal ulcers.

AXS-02, disodium zoledronate tetrahydrate, is a potentially first-in-class, oral, targeted, non-opioid therapeutic for chronic pain. AXS-02 is a potent inhibitor of osteoclasts, which are bone remodeling cells that break down bone tissue. We are developing AXS-02 for the treatment of pain in the following two conditions: knee OA associated with BMLs and CLBP associated with type 1 or mixed type 1 and type 2 MCs. These conditions exhibit target lesions or specific pathology that we believe may be addressed by the mechanisms of action of AXS-02, such as inhibition of osteoclast activity. These mechanisms may result in a reduction of pain in these conditions. We intend to seek FDA approval for AXS-02 utilizing the 505(b)(2) regulatory development pathway.

AXS-06, is a novel, oral, non-opioid, fixed-dose combination of MoSEIC™ meloxicam and esomeprazole. We are developing AXS-06 initially for the treatment of osteoarthritis and rheumatoid arthritis. Esomeprazole is a proton pump inhibitor which lowers stomach acidity and which has been shown to reduce the occurrence of NSAID-associated gastrointestinal ulcers. AXS-06 is designed to provide rapid, effective pain relief, and to reduce the risk of NSAID-associated gastrointestinal ulcers, with convenient once-daily dosing. We have successfully completed a Phase 1 trial of AXS-06 to characterize the pharmacokinetics of meloxicam and esomeprazole after oral administration of AXS-06. The results of our Phase 1 trial demonstrated that the median T_{max} for meloxicam, the trial's primary endpoint, was nine times faster for AXS-06 as compared to standard meloxicam. We intend to seek FDA approval for AXS-06 utilizing the 505(b)(2) regulatory development pathway.

Since our incorporation in January 2012, our operations to date have included organizing and staffing our company, business planning, raising capital, developing our compounds, and engaging in other discovery and preclinical activities. Prior to our initial public offering, or IPO, in November 2015, we financed our operations primarily through private placements of our convertible notes and subsequent to our IPO, through proceeds from sales of our common stock and warrants to purchase shares of our common stock to equity investors and debt borrowings. For a further discussion, see the section entitled “Liquidity and Capital Resources” below.

Our ability to become profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we obtain marketing approval for and successfully commercialize one of our product candidates.

We have incurred significant operating and net losses since inception. We incurred net losses of $31.0 million, $28.9 million, and $27.2 million for the years ended December 31, 2018, 2017, and 2016, respectively. Our accumulated deficit as of December 31, 2018 was $107.6 million, and we expect to incur significant expenses and increasing operating losses for the foreseeable future. We expect our expenses to increase in connection with our ongoing activities, as we continue the development and clinical trials of, and seek regulatory approval for our current product candidates and any other product candidates that we develop or in-license and advance to clinical development. If we obtain regulatory approval for a product candidate, we expect to incur significant expenses in order to create an infrastructure to support the commercialization of the product candidate, including manufacturing, sales, marketing, and distribution functions. Further, we have incurred and will continue to incur additional costs associated with operating as a public company. Accordingly, we will need additional financing to support our continuing operations. We will seek to fund our operations through public or private equity, debt financings, or other sources. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy. We will need to generate significant revenue to achieve profitability, and we may never do so.

Financial Overview

Revenue

We have not generated any revenue since we commenced operations and we do not expect to generate any revenue in the near future. To the extent we enter into licensing or collaboration arrangements, we may have sources of revenue in the future. We expect that any revenue we generate will fluctuate from quarter to quarter as a result of the amount and timing of payments that we may recognize upon the sale of our product candidates, to the extent that any product candidates are successfully commercialized, and the amount and timing of fees, reimbursements, and milestone and other payments received under any future licensing or collaboration arrangements. If we fail to complete the development of our product candidates in a timely manner or obtain regulatory approval for them, our ability to generate future revenue, and our results of operations and financial position, would be materially and adversely affected.

Research and Development Expenses

Research and development expenses primarily include preclinical studies, clinical trials, manufacturing costs, employee salaries and benefits, stock-based compensation expense; contract services, including external research and development expenses incurred under arrangements with third parties, such as contract research organizations, or CROs; facilities costs; overhead costs; depreciation; and other related costs.

Research and development activities are central to our business model. We will incur substantial costs beyond our present and planned clinical trials in order to file a new drug application, or NDA, for any of our product candidates. It is difficult to determine with certainty the costs and duration of our current or future clinical trials and preclinical studies, or if, when, or to what extent we will generate revenue from the commercialization and sale of our product candidates if we obtain regulatory approval. We may never succeed in achieving regulatory approval. The duration, costs, and timing of clinical trials and development of our product candidates will depend on a variety of factors, including the uncertainties of future clinical trials and preclinical studies, uncertainties in clinical trial enrollment rate, and significant and changing government regulation. In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing capability, and commercial viability. We will determine which programs to pursue and how much to fund each program in response to the scientific and clinical success of each product candidate, as well as an assessment of each product candidate's commercial potential. Management considers many factors in developing the estimates and assumptions that are used in the preparation of these financial statements.

Management must apply significant judgment in this process. In addition, other factors may affect estimates, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made.

The following table summarizes our research and development expenses by program for the years ended December 31, 2018, 2017, and 2016:

	Year ended December 31,		
	2018	2017	2016
AXS-05	$ 13,460,809	$ 9,780,593	$ 8,444,618
AXS-07	3,222,208	180,255	—
AXS-12	193,459	—	—
AXS-02	740,341	6,775,736	9,414,980
AXS-06	71,164	480,425	353,957
Other research and development	5,415,127	2,126,978	1,870,679
Stock-based compensation	391,946	613,629	1,115,626
Total research and development expenses	$ 23,495,055	$ 19,957,616	$ 21,199,860

Other research and development expenses primarily consist of employee salaries and benefits, facilities and overhead costs, and expenses for terminated programs. For the **year** ended December 31, 2018, all employee salaries and benefits were allocated to Other research and development expenses whereas for the year ended 2017 and 2016, a majority of employee salaries and benefits were allocated to the respective programs.

General and Administrative Expenses

General and administrative expenses primarily consist of salaries and related costs for personnel in executive, finance, and operational functions, including stock-based compensation and travel expenses. Other general and administrative expenses include facility-related costs, insurance expense, and professional fees for legal and accounting services and patent filing and prosecution costs. General and administrative expenses are expensed when incurred.

Interest and Amortization of Debt Discount Expense

Interest and amortization of debt discount expense primarily consists of cash interest and non-cash costs related to our original term loan and loan amendment with SVB, which was originally entered into in November 2016 and amended in November 2018 (see “Liquidity and Capital Resources” below for a further discussion).We amortize these costs over the term of our debt agreements as interest expense in our consolidated statement of operations. Interest and amortization of debt discount expense also includes interest income earned on cash.

Tax Credit

The tax credits represent the receipt of the New York City Biotechnology Tax Credit, or NYC Biotech credit, and receipt by Axsome Therapeutics Australia PTY, LTD, our Australian subsidiary, of the Australia Tax Incentive Credit, related to allowable research and development expenses incurred for our product candidates.

Change in Fair Value of Warrant Liability

The warrants to purchase our common stock issued as part of the registered direct stock offering in December 2017 were classified as a warrant liability and recorded at fair value. The warrant liability was subject to re-measurement at each balance sheet date and any change in fair value was recognized in our statements of operations as a change in fair value of the warrant liability. The warrants expired on December 11, 2018.

Critical Accounting Policies and Significant Judgments and Estimates

This discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States of America, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of expenses during the reported period. In accordance with GAAP, we base our estimates on historical experience and on various other assumptions that we believe are reasonable under the circumstances. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are more fully described in Note 2 to our audited consolidated financial statements appearing elsewhere in this report, we believe the following accounting policies are the most critical to the judgments and estimates we use in the preparation of our consolidated financial statements.

Research and Development Expenses

Generally, research and development costs are expensed as incurred. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and amortized over the period that the goods are delivered or the related services are performed, subject to an assessment of recoverability. We make estimates of costs incurred in relation to external CROs and clinical site costs. We analyze the progress of clinical trials, including levels of patient enrollment, invoices received and contracted costs when evaluating the adequacy of the amount expensed and the related prepaid asset and accrued liability. Significant judgments and estimates must be made and used in determining the accrued balance and expense in any accounting period. We review and accrue CRO expenses and clinical trial study expenses based on work performed and rely upon estimates of those costs applicable to the stage of completion of a study. Accrued costs are subject to revisions as such trials progress to completion. Revisions are charged to expense in the period in which the facts that give rise to the revision become known. With respect to clinical site costs, the financial terms of these agreements are subject to negotiation and vary from contract to contract. Payments under these contracts may be uneven, and depend on factors such as the achievement of certain events, the successful recruitment of patients, the completion of portions of the clinical trial or similar conditions. The objective of our policy is to match the recording of expenses in our financial statements to the actual services received and efforts expended. As such, expense accruals related to clinical site costs are recognized based on our estimate of the degree of completion of the event or events specified in the specific clinical study or trial contract.

Income Taxes

Income taxes are accounted for under the asset and liability method. Under this method, deferred tax assets and liabilities are recognized for the future tax consequences attributable to the differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases, operating losses, and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period that includes the enactment date. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

We recognize the tax benefit from an uncertain tax position only if it is more likely than not to be sustained upon examination based on the technical merits of the position as well as consideration of the available facts and circumstances. When uncertain tax positions exist, we recognize the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. As of December 31, 2018, we do not believe any material uncertain tax positions are present.

As of December 31, 2018, we had U.S. federal net operating loss, or NOL carryforwards of approximately $87 million. NOLs amounting to $60 million generated before the 2018 tax year will start expiring beginning 2033, and the NOLs of approximately $27 million generated in 2018 have an indefinite carryforward period.

Utilization of the net operating losses may be subject to a substantial annual limitation due to ownership change limitations provided by the Internal Revenue Code of 1986, as amended. The annual limitation for net operating losses incurred before the 2018 tax year may result in expiration before we can use them. We have recorded a valuation allowance on all of our deferred tax assets.

On December 22, 2017, the U.S. President signed the Tax Cuts and Jobs Act, or the Act, into law. Effective January 1, 2018, among other changes, the Act (1) reduces the U.S. federal corporate tax rate from 35 percent to 21 percent, (2) changes the rules relating to net operating loss, or NOL, carryforwards and carrybacks, (3) eliminates the corporate alternative minimum tax, or AMT, and changes how existing AMT credits can be realized; and (4) requires companies to pay a one-time transition tax on certain unrepatriated earnings of foreign subsidiaries.

Stock-based compensation

For issued stock options, we estimate the grant date fair value of each option using the Black-Scholes option pricing model. The Black-Scholes model takes into account the expected volatility of our common stock, the risk-free interest rate, the estimated life of the option, the closing market price of our common stock and the exercise price. The estimates utilized in the Black-Scholes calculation involve inherent uncertainties and the application of management judgment. In addition, we recognize expense for equity award forfeitures as they occur. For awards subject to service-based vesting conditions, we recognize stock-based compensation expense on a straight-line basis over the requisite service period, which is generally the vesting term. For awards subject to performance-based vesting conditions, we recognize stock-based compensation expense using the accelerated attribution method when it is probable that the performance condition will be achieved. The expense related to the stock-based compensation is recorded within the financial statement line item the grantee's cash compensation is recorded in.

Our policy upon exercise of stock options is that shares will be issued as new shares drawing on our 2015 Omnibus Incentive Compensation Plan share pool that was adopted by the stockholders in November 2015.

Results of Operations

Comparison of the Years Ended December 31, 2018 and 2017

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

	Year ended December 31,	
	2018	2017
Operating expenses:		
Research and development	$ 23,495,055	$ 19,957,616
General and administrative	9,351,522	7,206,691
Total operating expenses	32,846,577	27,164,307
Loss from operations	(32,846,577)	(27,164,307)
Interest and amortization of debt discount expense	(1,127,305)	(1,340,199)
Tax credit	217,418	207,114
Change in fair value of warrant liability	2,791,000	(646,000)
Net loss	$ (30,965,464)	$ (28,943,392)

Research and Development Expenses. Our research and development expenses for the year ended December 31, 2018 were $23.5 million, compared to $20.0 million for the year ended December 31, 2017, an increase of $3.5 million. The increase was primarily due to increased costs for our STRIDE-1 and ADVANCE-1 studies, initiation and completion of our ASCEND study, and AXS-07 and AXS-12 study startup and manufacturing costs, which was partially offset by a reduction in the costs of our clinical trials for AXS-02 and AXS-05 and nonclinical work on AXS-05.

General and Administrative Expenses. Our general and administrative expenses for the year ended December 31, 2018 were $9.4 million, as compared to $7.2 million for the year ended December 31, 2017, an increase of $2.2 million. The increase was primarily due to higher intellectual property costs and legal expenses, external fees associated with operating as a public company, as well as an increase in personnel costs.

Interest and Amortization of Debt Discount Expense. Interest and amortization of debt discount expense for the year ended December 31, 2018 was $1.1 million, as compared to $1.3 million for the year ended December 31, 2017, a decrease of $0.2 million. The decrease was primarily related to lower interest expense and amortization of the debt discount associated with our loan and security agreement with SVB due to a lower principal balance.

Tax Credit. Tax credit income for the year ended December 31, 2018 and 2017 was $0.2 million and represents the receipt by Axsome Therapeutics Australia PTY LTD, our Australian subsidiary, of the Australia Tax Incentive Credit related to the 2017 and 2016 research and development expenses incurred for our product candidates.

Change in Fair Value of Warrant Liability. For the year ended December 31, 2018, we recorded income of $2.8 million from the change in fair value of our warrant liability in connection with the warrants issued as part of our December 2017 registered direct offering. The change in fair value is due to the decrease of our closing stock price over the course of the year, from when the warrants were initially issued. For the year ended December 31, 2017, we recorded expense of $0.6 million.

Comparison of the Years Ended December 31, 2017 and 2016

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

	Year ended December 31,	
	2017	2016
Operating expenses:		
Research and development	$ 19,957,616	$ 21,199,860
General and administrative	7,206,691	6,343,648
Total operating expenses	27,164,307	27,543,508
Loss from operations	(27,164,307)	(27,543,508)
Interest and amortization of debt discount expense	(1,340,199)	(132,424)
Tax credit	207,114	474,279
Change in fair value of warrant liability	(646,000)	—
Net loss	$ (28,943,392)	$ (27,201,653)

Research and Development Expenses. Our research and development expenses for the year ended December 31, 2017 were $20.0 million, compared to $21.2 million for the year ended December 31, 2016, a decrease of $1.2 million. The decrease was primarily due to the lower costs of our previously initiated clinical trials, offset by the initiation of our ADVANCE-1 study as well as an increase in personnel costs and stock compensation expense.

General and Administrative Expenses. Our general and administrative expenses for the year ended December 31, 2017 were $7.2 million, as compared to $6.3 million for the year ended December 31, 2016, an increase of $0.9 million. The increase was primarily due to higher intellectual property costs, stock compensation expense and placement agent expenses associated with our registered direct offering completed in December 2017.

Interest and Amortization of Debt Discount Expense. Interest and amortization of debt discount expense for the year ended December 31, 2017 was $1.3 million, as compared to $0.1 million for the year ended December 31, 2016, an increase of $1.2 million. The increase was related to interest and the amortization of the debt discount associated with our loan and security agreement with SVB which began in November 2016.

Tax Credit. During the year ended December 31, 2017, the income of $0.2 million represents the receipt by Axsome Therapeutics Australia PTY LTD, our Australian subsidiary, of the Australia Tax Incentive Credit related to the 2016 research and development expenses for our product candidates. In 2016, we received the NYC Biotech credit in the amount of $0.5 million related to the research and development expenses of our product candidates.

Change in Fair Value of Warrant Liability. We recorded expense related to the change in fair value of our warrant liability for the year ended December 31, 2017 of $0.6 million. There was no warrant liability recorded during the year ended December 31, 2016.

Liquidity and Capital Resources

In November 2015, we completed our IPO, in which we sold 5,666,667 shares of common stock at an offering price to the public of $9.00 per share. We received gross proceeds of approximately $51.0 million and net proceeds of approximately $45.5 million, after deducting underwriting discounts and commissions and offering-related transaction costs.

In November 2016, we entered into a loan and security agreement with SVB for a term loan of up to $20.0 million, which we refer to as the Original Term Loan.. The initial tranche of $10.0 million was funded shortly after executing the loan agreement. Because we did not achieve the conditional criteria to access the second and third tranches before the specified dates, the $10.0 million in additional term loan advances expired. In November 2018, we amended the loan and security agreement with SVB to provide an additional $4 million growth capital loan, related to our narcolepsy clinical program with AXS-12. We refer to this amendment as the First Amendment to the Original Term Loan. The additional capital was available to be drawn, at our option, subject to the achievement of a specified clinical milestone. Our obligations under the loan and security agreement, as amended, along with our ability to draw down on the additional $4.0 million tranche, were subsequently extinguished in connection with the establishment of a new term loan facility with SVB during March 2019 (see below).

On December 1, 2016, we filed a shelf registration statement with the SEC for the issuance of common stock, preferred stock, warrants, rights, debt securities and units up to an aggregate amount of $150.0 million, which we refer to as the 2016 Shelf Registration Statement. On December 16, 2016, the 2016 Shelf Registration Statement was declared effective by the SEC. As discussed in greater detail below, we completed an offering of common stock in March 2017, entered into a sales agreement in October 2017 pursuant to which we sold shares of our common stock from time to time in an at-the-market offering until completion of the offering in January 2019, and completed a registered direct offering priced at the market in December 2017 and September 2018, each utilizing the 2016 Shelf Registration Statement. In the future, we may conduct additional offerings of one or more of these securities utilizing the 2016 Shelf Registration Statement in such amounts, prices and terms to be announced when and if the securities are offered. At the time any of our securities covered by the 2016 Shelf Registration Statement are offered for sale, a prospectus supplement will be prepared and filed with the SEC containing specific information about the terms of any such offering.

In March 2017, we completed an underwritten public offering, whereby we sold 4,304,813 shares of our common stock at a public offering price of $3.74 per share. We received gross proceeds of approximately $16.1 million and net proceeds of approximately $14.8 million, net of underwriting discounts and offering expenses.

In October 2017, we entered into an “at-the-market” sales agreement, or the Sales Agreement, with Leerink Partners LLC, or Leerink, pursuant to which we could sell up to $30 million in shares of our common stock from time to time through Leerink, acting as our sales agent, in one or more at-the-market offerings. We received approximately $4.2 million in gross proceeds from the sales of our common stock to Leerink under the Sales Agreement during the year ended December 31, 2018. In January 2019, we raised approximately $25.8 million in gross proceeds through the sale of 3,164,015 shares under the Sales Agreement. Upon completion of the final sale, the Sales Agreement was automatically terminated. Leerink received a commission of 3.0% of the gross proceeds for all shares sold under the Sales Agreement.

In December 2017, we completed a registered direct offering priced at the market, whereby we sold an aggregate of $9.5 million worth of units, or Units, at a purchase price of $5.325 per Unit, with each Unit consisting of (i)one share of our common stock, and (ii) a warrant to purchase one share of our common stock, or Common Warrant, at an exercise price equal to $5.25 per share. We sold an aggregate of 1,783,587 Units in the offering for gross proceeds of approximately $9.5 million and net proceeds of approximately $8.8 million, net of underwriting discounts and offering expenses. Additionally, we issued warrants to purchase up to 107,015 shares of our common stock at an exercise price of $6.6562 per share to certain investors affiliated with H.C. Wainwright & Co., LLC, placement agent for the offering, which we refer to as the Placement Agent Warrants. The Placement Agent Warrants have the same terms as the Common Warrants, except for the difference in exercise price noted above. Both the Common Warrants and the Placement Agent Warrants expired on December 11, 2018.

On September 27, 2018, we entered into a purchase agreement with certain institutional and accredited investors, which we refer to as the RDO Investors, for the sale by us directly to the RDO Investors of an aggregate of 2,966,667 shares of the our common stock, at a purchase price of $3.00 per share, which we refer to as the 2018 Registered Direct Offering, for gross proceeds of approximately $8.9 million. The 2018 Registered Direct Offering closed on October 1, 2018, and we received net proceeds of approximately $8.8 million, after deducting transaction expenses. The 2,966,667 shares of common stock sold in the 2018 Registered Direct Offering were offered and sold by us directly to the RDO Investors, without a placement agent, underwriter, broker or dealer, pursuant to a prospectus supplement to the 2016 Shelf Registration Statement.

In March 2019, we entered into a loan and security agreement with SVB and WestRiver Innovation Lending Fund VIII, L.P., or WestRiver, for a term loan up to $24.0 million, which completely replaces the Original Term Loan and the First Amendment to the Original Term Loan. The initial tranche of $20.0 million was funded shortly after executing the loan agreement. The second tranche of $4.0 million is available to be drawn, at our option, subject to the achievement of positive data, on or prior to August 15, 2019, with respect to our ongoing Phase 2 clinical trial for AXS-12 in narcolepsy, sufficient to submit a Phase 3 protocol to FDA, provided that we have not received any objections from the FDA within thirty days after submission of such Phase 3 protocol A portion of the initial tranche was used to satisfy our existing obligations under our November 2016 term loan facility with SVB, as amended in November 2018, and such obligations are considered fully repaid and extinguished.

We believe our current cash, which includes proceeds from the January 2019 at-the-market equity financings and the March 2019 term loan, will be sufficient to fund our anticipated operating cash requirements into at least the fourth quarter of 2021. Because the process of evaluating product candidates in clinical trials is costly and the timing of progress in these trials is uncertain, it is possible that the assumptions upon which we have based this estimate may prove to be wrong, and we could use our capital resources sooner than we currently expect.

Cash Flows

The following table summarizes our primary sources and uses of cash for the periods indicated:

	Year ended December 31,		
	2018	**2017**	**2016**
Net cash (used in) provided by:			
Operating activities	$ (30,053,701)	$ (26,471,652)	$ (21,281,304)
Investing activities	(32,696)	(9,898)	(104,561)
Financing activities	10,034,016	23,884,176	9,968,102
Net increase (decrease) in cash	$ (20,052,381)	$ (2,597,374)	$ (11,417,763)

Operating Activities. Net cash used in operating activities for the year ended December 31, 2018 was $30.1 million as compared to $26.5 million for the year ended December 31, 2017. The increase of $3.6 million in net cash used was primarily related to an increase in operating expenses in 2018 compared to 2017 for ADVANCE-1, STRIDE-1, and ASCEND clinical trials, offset by increase in change in operating liabilities.

Net cash used in operating activities for the year ended December 31, 2017 was $26.5 million as compared to $21.3 million for the year ended December 31, 2016. The increase of $5.2 million in net cash used was primarily related to a reduction in accounts payable and accrued expenses and an increase in general and administrative expenses, which includes $0.2 million in placement agent expense associated with our registered direct offering in December 2017.

Investing Activities. Cash used in investing activities for the purchase of equipment was less than $0.1 million for the year ended December 31, 2018 and December 31, 2017. Cash used in investing activities was $0.1 million for the year ended December 31, 2016.

Financing Activities. Net cash provided by financing activities for the year ended December 31, 2018 was $10.0 million, which includes net proceeds from the sale of common stock in the October 2018 registered direct offering of $8.8 million, $4.1 million in proceeds from sales made through at-the-market offerings, as well as $0.5 million from the exercise of options and warrants, partially offset by principal repayment on our term loan of $3.3 million.

Net cash provided by financing activities for the year ended December 31, 2017 was $23.9 million, which included the net proceeds from the sale of common stock in the March 2017 public offering of $14.8 million, the December 2017 registered direct offering of $8.8 million, $0.1 million in proceeds from sales made through at-the-market offerings, as well as $0.5 million from the exercise of options and warrants, partially offset by principal repayment on our November 2016 term loan with SVB of $0.3 million. Net cash provided by financing activities for the year ended December 31, 2016 was $10.0 million, which consisted of the net proceeds received from our November 2016 term loan with SVB..

Funding requirements

We have not achieved profitability since our inception and we expect to continue to incur significant losses for the foreseeable future. We expect our losses to increase as we continue the development of and seek regulatory approvals for our product candidates and begin to commercialize any approved products. We are subject to all of the risks pertinent to the development of new product candidates, and we may encounter unforeseen expenses, difficulties, complications, delays, and other unknown factors that may harm our business.

We anticipate that we will need to raise substantial additional financing in the future to fund our operations. In order to meet these additional cash requirements, we may incur debt, license certain intellectual property, and seek to sell additional equity or convertible securities that may result in dilution to our stockholders. If we raise additional funds through the issuance of equity or convertible securities, these securities could have rights or preferences senior to those of our common stock and could contain covenants that restrict our operations. There can be no assurance that we will be able to obtain additional equity or debt financing on terms acceptable to us, if at all. Our future capital requirements will depend on many factors, including:

- the scope, rate of progress, results, and cost of our clinical studies and other related activities;
- our ability to enter into collaborative agreements for the development and commercialization of our product candidates;
- the number and development requirements of any other product candidates that we pursue;
- the costs, timing, and outcome of regulatory reviews of our product candidates;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales, and distribution, for any of our product candidates for which we receive marketing approval;
- any product liability or other lawsuits related to our product candidates;
- the expenses needed to attract and retain skilled personnel;
- the general and administrative expenses related to being a public company;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval; and
- the costs involved in preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property rights, and defending our intellectual property-related claims.

Please see “Risk Factors” for additional risks associated with our substantial capital requirements.

Contractual Obligations and Commitments

The following is a summary of our contractual obligations as of December 31, 2018:

(in thousands)	Total	Less than one year	1 - 3 years	3 - 5 years	More than 5 years
Term loan	$ 6,981,944	$ 3,797,299	$ 3,184,645	$ —	$ —
Total contractual obligations	$ 6,981,944	$ 3,797,299	$ 3,184,645	$ —	$ —

Under three exclusive license agreements with Antecip Bioventures II LLC, or Antecip, an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., we are obligated to make specified royalty payments ranging from 1.5% to 4.5%, subject to up to a 50% reduction depending on required payments to third parties, on net sales of licensed products. The amount, timing, and likelihood of such payments are not known. For a more detailed description of these agreements, please see “Business—Material License Agreements.”

November 2016 Loan and Security Agreement—Silicon Valley Bank

In November 2016, we entered into a loan and security agreement with Silicon Valley Bank, or SVB, for a term loan of up to $20.0 million. The initial tranche of $10.0 million was funded shortly after executing the loan agreement. We were scheduled to make interest only payments on the loan until December 1, 2017, which could have been extended under certain circumstances. Under the terms of the loan, we had the opportunity, but not the obligation to, draw two additional tranches of $5.0 million each prior to November 9, 2017 and December 31, 2017, subject to the achievement of certain clinical and financial milestones. Because we did not achieve the conditional criteria to access the second and third tranches before the specified dates, the $10.0 million in additional term loan advances expired.

The SVB loan accrued interest at an annual rate equal to 4.50% plus the prime rate, which was the greater of 3.50% or the Wall Street Journal prime rate, and was payable monthly. Following the interest only payment period, we began making monthly payments of principal and interest. In addition, we were required to pay a final payment fee of 8.5% of the principal amount extended to us on the date of repayment of the outstanding loan.

We were permitted to prepay all, but not less than all, of the SVB loan subject to a prepayment premium of 3.0% of the outstanding principal if prepaid within two years of the effective date of the loan, 2.0% of the outstanding principal if prepaid during the third year of the loan, and 1.0% of the outstanding principal if prepaid after the third year. The term loan was collateralized by a security interest in all of our assets except intellectual property. Our intellectual property was subject to a negative pledge.

In connection with the loan, SVB and Life Science Loans, LLC, received warrants to purchase an aggregate 65,228 shares of our common stock at an exercise price of $7.41 per share, which are exercisable for seven years from the date of issuance.

We allocated the proceeds of $10.0 million based on the relative fair values of the debt instrument and the warrant instrument. The relative fair value of the warrants of approximately $0.3 million at the time of issuance, which was determined using the Black-Scholes option-pricing model, was recorded as additional paid-in capital and reduced the carrying value of the debt. The discount on the debt was being amortized to interest expense over the term of the debt.

In November 2018, we amended the loan and security agreement with SVB to provide an additional $4 million growth capital loan, related to our narcolepsy clinical program with AXS-12. The additional capital was available to be drawn, at our option, subject to the achievement of a specified clinical milestone. Our obligations under the loan and security agreement, as amended, along with the ability to draw down on the additional $4.0 million tranche, were subsequently extinguished in connection with the establishment of a new term loan facility with SVB during March 2019.

Shelf Registration Statement

On December 1, 2016, we filed the 2016 Shelf Registration Statement with the SEC for the issuance of common stock, preferred stock, warrants, rights, debt securities and units up to an aggregate amount of $150.0 million. On December 16, 2016, the 2016 Shelf Registration Statement was declared effective by the SEC. At the time any of the securities covered by the 2016 Shelf Registration Statement are offered for sale, a prospectus supplement will be prepared and filed with the SEC containing specific information about the terms of any such offering.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined by applicable SEC regulations.

JOBS Act

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards, and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Recent Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU No. 2016-02, Leases (Topic 842), which supersedes FASB Topic 840, Leases (Topic 840), requires that assets and liabilities arising under leases be recognized on the balance sheet as well as additional quantitative and qualitative disclosures that provide the amount, timing, and uncertainty of cash flows related to lease agreements. In July 2018, the FASB also issued ASU No. 2018-11, Leases (Topic 842), which provides (1) optional transition method that entities can use when adopting the standard and (2) a practical expedient that permits lessors to not separate nonlease components from the associated lease component if certain conditions are met. The standard is effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted upon issuance. We elected to use the transition method approved by the FASB in accordance with ASU No. 2018-11, Leases, which allows companies to apply the provisions of the new leasing standard as of January 1, 2019, without adjusting the comparative periods presented by recognizing a cumulative-effect adjustment to the opening balance of retained earnings. We applied a policy election to exclude short-term leases from balance sheet recognition and also elected certain practical expedients at adoption. As permitted under these expedients, we did not reassess whether existing contracts are or contain leases, the lease classification for any existing leases, initial direct costs for any existing lease and whether existing land easements and rights of way, that were not previously accounted for as leases, are or contain a lease. Although we are still finalizing its evaluation of the standard update and the quantification of its impact, we expect its adoption will not have a material impact on our financial statements.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows (Topic 230) – Classification of Certain Cash Receipts and Cash Payments*, which is guidance to address diversity in practice with respect to how certain cash receipts and cash payments are presented and classified in the statement of cash flows. The updated guidance addresses eight specific cash flow issues with the objective of reducing the existing diversity that occurs in practice. The guidance is effective for annual and interim periods beginning after December 15, 2017. We have adopted this guidance effective January 1, 2018 and the adoption of the guidance did not have a material impact to our financial statements.

In May 2017, the FASB issued No. ASU 2017-09, *Compensation-Stock Compensation (Topic 718): Scope of Modification Accounting*. ASU 2017-09 provides clarity and reduces both (1) diversity in practice and (2) cost and complexity when applying the guidance in Topic 718, to a change to the terms or conditions of a share-based payment award. The amendments in ASU 2017-09 should be applied prospectively to an award modified on or after the adoption date. This ASU is effective for fiscal years beginning after December 15, 2017, including interim periods within those years. We have adopted this guidance effective January 1, 2018 and the adoption of the guidance did not have a material impact to our financial statements.

In June 2018, the FASB issued No. ASU 2018-07, *Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* to simplify the accounting for share-based payments to nonemployees by aligning it with the accounting for share-based payments to employees, with certain exceptions. The standard will be effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted upon issuance. We have adopted this guidance effective October 1, 2018 and the adoption of the guidance did not have a material impact on our financial statements.

In July 2018, the FASB issued ASU No. 2018-09, Codification Improvements, which provides technical corrections, clarifications, and other improvements to several topics in the FASB Accounting Standard Codification. The transition and effective date guidance is based on the facts and circumstances of each amendment. Some of the amendments do not require transition guidance and were effective upon issuance of the ASU. Amendments that do not have transition guidance are effective for annual periods beginning after December 15, 2018. We are currently evaluating the potential impact of the new guidance.

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*, which modifies, removes and adds certain disclosure requirements on fair value measurements based on the FASB Concepts Statement, *Conceptual Framework for Financial Reporting-Chapter 8: Notes to the Financial Statements*. The amendments on changes in unrealized gains and losses, the range and weighted average of significant unobservable inputs used to develop Level 3 fair value measurements and the narrative description of measurement uncertainty should be applied prospectively for only the most recent interim or annual period presented in the initial fiscal year of adoption. All other amendments should be applied retrospectively to all periods presented upon their effective date. The ASU is effective for fiscal years beginning after December 15, 2019, including interim periods within those years. We are currently evaluating the potential impact of the new guidance.

In August 2018, the SEC adopted the final rule under SEC Release No. 33-10532, *Disclosure Update and Simplification*, amending certain disclosure requirements that were redundant, duplicative, overlapping, outdated or superseded. The changes are generally expected to reduce or eliminate certain disclosures; however, the amendments did expand interim period disclosure requirements related to changes in stockholders' equity. The final rule is effective on November 5, 2018 and the adoption of the guidance did not have a material impact on our financial statements.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURE ABOUT MARKET RISK

Interest Rate Risk

We are exposed to market risks in the ordinary course of our business. These market risks are principally limited to interest rate fluctuations. We had cash of $14.0 million as of December 31, 2018. The primary objective of our investment activities is to preserve principal and liquidity while maximizing income without significantly increasing risk. We do not enter into investments for trading or speculative purposes. Due to the short-term nature of our investment portfolio, we do not believe an immediate 10% increase in interest rates would have a material effect on the fair market value of our portfolio, and, accordingly, we do not expect our operating results or cash flows to be materially affected by a sudden change in market interest rates.

Foreign Currency Exchange Risk

We contract with vendors and third-party manufacturers in several foreign countries. Several of these contracts are denominated in Euros, British pounds, and Australian dollars. We are therefore subject to fluctuations in foreign currency rates in connection with these agreements, and recognize foreign exchange gains or losses in our statement of operations. We have not historically hedged our foreign currency exchange rate risk. To date, we have not incurred any material effects from foreign currency changes on these contracts.

We do not believe a 10% change in these currencies on December 31, 2018 would have had a material effect on our results of operations or financial condition.

Inflation Risk

Inflation generally affects us by increasing our cost of labor and pricing of contracts. We do not believe that inflation has had a material effect on our business, financial condition, or results of operations during the year ended December 31, 2018.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA.

Our consolidated financial statements and the notes thereto, included in Part IV, Item 15(a), part 1, are incorporated by reference into this Item 8.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE.

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures. Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2018. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, mean controls and other procedures of a company that are designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to management, including our principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. 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. Based on the evaluation of our disclosure controls and procedures as of December 31, 2018, our principal executive officer and principal financial officer concluded that, as of such date, our disclosure controls and procedures were effective.

Management's Annual Report on Internal Control over Financial Reporting. Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rule 13a-15(f) or Rule 15d-15(f) under the Exchange Act). Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, our management used the criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission, or COSO Framework. Our management has concluded that, as of December 31, 2018, our internal control over financial reporting was effective based on these criteria.

This annual report does not include an attestation report of our independent registered public accounting firm regarding internal control over financial reporting. Management's report was not subject to the attestation by our independent registered public accounting firm because emerging growth companies are exempt from this requirement.

Inherent Limitations on Effectiveness of Controls. Our management, including our principal executive officer and principal financial officer, does not expect that our disclosure controls and procedures will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefits of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within our Company have been detected.

ITEM 9B. OTHER INFORMATION.

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE.

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2018 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION.

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2019 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS.

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2019 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS AND DIRECTOR INDEPENDENCE.

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2019 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES.

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2019 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

PART IV

ITEM 15. EXHIBITS and FINANCIAL STATEMENT SCHEDULES.

(a)1. Consolidated Financial Statements

The following consolidated financial statements of Axsome Therapeutics, Inc. are filed as part of this report.

2. Consolidated Financial Statement Schedules

All schedules are omitted as the information required is inapplicable or the information is presented in the consolidated financial statements or the related notes.

3. Exhibits

The list of exhibits filed with this report is set forth in the Exhibit Index following the signature page and is incorporated herein by reference.

Axsome Therapeutics, Inc.
Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Axsome Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Axsome Therapeutics, Inc. (the "Company") as of December 31, 2018 and 2017, the related consolidated statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2018, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

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

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2014.
New York, New York
March 14, 2019

Axsome Therapeutics, Inc.
Consolidated Balance Sheets

	December 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash	$ 13,968,742	$ 34,021,123
Prepaid and other current assets	1,246,360	1,278,418
Total current assets	15,215,102	35,299,541
Equipment, net	51,832	68,071
Other assets	112,345	187,952
Total assets	$ 15,379,279	$ 35,555,564
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 3,687,245	$ 3,435,456
Accrued expenses and other current liabilities	3,843,299	2,679,534
Loan payable, current portion	3,291,394	3,269,346
Warrant liability	—	2,791,000
Total current liabilities	10,821,938	12,175,336
Loan payable, long-term	3,619,420	6,663,005
Total liabilities	14,441,358	18,838,341
Stockholders' equity:		
Preferred stock, $0.0001 par value per share (10,000,000 shares authorized, none issued and outstanding at December 31, 2018 and December 31, 2017, respectively)	—	—
Common stock, $0.0001 par value per share (150,000,000 shares authorized, 30,087,213 and 25,492,992 shares issued and outstanding at December 31, 2018 and December 31, 2017, respectively)	3,009	2,549
Additional paid-in capital	108,485,219	93,299,517
Accumulated deficit	(107,550,307)	(76,584,843)
Total stockholders' equity	937,921	16,717,223
Total liabilities and stockholders' equity	$ 15,379,279	$ 35,555,564

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

Axsome Therapeutics, Inc.
Consolidated Statements of Operations

	Year ended December 31,		
	2018	2017	2016
Operating expenses:			
Research and development	$ 23,495,055	$ 19,957,616	$ 21,199,860
General and administrative	9,351,522	7,206,691	6,343,648
Total operating expenses	32,846,577	27,164,307	27,543,508
Loss from operations	(32,846,577)	(27,164,307)	(27,543,508)
Interest and amortization of debt discount expense	(1,127,305)	(1,340,199)	(132,424)
Tax credit	217,418	207,114	474,279
Change in fair value of warrant liability	2,791,000	(646,000)	—
Net loss	$ (30,965,464)	$ (28,943,392)	$ (27,201,653)
Net loss per common share, basic and diluted	$ (1.15)	$ (1.27)	$ (1.42)
Weighted average common shares outstanding, basic and diluted	26,883,656	22,764,606	19,150,690

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

Axsome Therapeutics, Inc.
Consolidated Statements of Stockholders' Equity

	Common stock		Additional paid-in capital	Accumulated deficit	Total stockholders' equity
	Shares	Amount			
Balance at December 31, 2015	19,149,417	1,915	66,882,144	(20,439,798)	$ 46,444,261
Stock-based compensation	—	—	2,031,418	—	2,031,418
Proceeds from exercise of options	9,000	1	33,029	—	33,030
Issuance of warrants	—	—	264,395	—	264,395
Net loss	—	—	—	(27,201,653)	(27,201,653)
Balance at December 31, 2016	19,158,417	1,916	69,210,986	(47,641,451)	21,571,451
Stock-based compensation	—	—	2,072,210	—	2,072,210
Proceeds from exercise of options	88,922	9	316,710	—	316,719
Exercise of warrants	129,149	13	167,881	—	167,894
Issuance of common stock upon financing	6,116,504	611	21,531,730	—	21,532,341
Net loss	—	—	—	(28,943,392)	(28,943,392)
Balance at December 31, 2017	25,492,992	2,549	93,299,517	(76,584,843)	16,717,223
Stock-based compensation	—	—	1,754,974	—	1,754,974
Issuance of common stock upon exercise of options	278,925	29	380,293	—	380,322
Exercise of warrants	101,310	10	131,693	—	131,703
Issuance of warrants upon debt financing	—	—	37,842	—	37,842
Issuance of common stock upon financing	4,213,986	421	12,880,900	—	12,881,321
Net loss	—	—	—	(30,965,464)	(30,965,464)
Balance at December 31, 2018	30,087,213	$ 3,009	$ 108,485,219	$ (107,550,307)	$ 937,921

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

Axsome Therapeutics, Inc.
Consolidated Statements of Cash Flows

	Year ended December 31,		
	2018	2017	2016
Cash flows from operating activities			
Net loss	$ (30,965,464)	$ (28,943,392)	$ (27,201,653)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	1,754,974	2,072,210	2,031,418
Amortization of debt discount	375,635	470,521	68,930
Change in fair value of warrants	(2,791,000)	646,000	—
Depreciation	48,935	42,557	20,484
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	32,058	102,143	(383,942)
Other assets	75,607	(75,131)	(86,196)
Accounts payable	251,789	(645,717)	2,188,810
Accrued expenses and other current liabilities	1,163,765	(140,843)	2,080,845
Net cash used in operating activities	(30,053,701)	(26,471,652)	(21,281,304)
Cash flows from investing activities			
Purchases of equipment	(32,696)	(9,898)	(104,561)
Net cash used in investing activities	(32,696)	(9,898)	(104,561)
Cash flows from financing activities			
Proceeds from issuance of term loan	—	—	10,000,000
Payment of debt issuance costs	(25,997)	—	(64,928)
Repayment of principal on term loan	(3,333,333)	(277,778)	—
Proceeds from issuance of common stock upon financing, net	12,881,321	23,677,341	—
Proceeds from issuance of common stock upon exercise of warrants	131,703	167,894	33,030
Proceeds from issuance of common stock upon exercise of options	380,322	316,719	—
Net cash provided by financing activities	10,034,016	23,884,176	9,968,102
Net (decrease) increase in cash	(20,052,381)	(2,597,374)	(11,417,763)
Cash at beginning of period	34,021,123	36,618,497	48,036,260
Cash at end of period	$ 13,968,742	$ 34,021,123	$ 36,618,497
Supplemental disclosures of cash flow information:			
Interest paid	$ 771,966	$ 865,278	$ 46,667
Supplemental disclosures of non-cash financing activity:			
Establishment of warrant liabilities in connection with common stock issuance	$ —	$ 2,145,000	$ —
Issuance of warrants in connection with debt financing	$ 37,842	$ —	$ 264,395

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

Axsome Therapeutics, Inc.
Notes to Consolidated Financial Statements

Note 1. Nature of Business and Basis of Presentation

Axsome Therapeutics, Inc. ("Axsome" or the "Company") is a clinical-stage biopharmaceutical company developing novel therapies for central nervous system ("CNS") disorders for which there are limited treatment options. By focusing on this therapeutic area, the Company is addressing significant and growing markets where current treatment options are limited or inadequate. The Company's core CNS portfolio includes four product candidates, AXS-05, AXS-07, AXS-09, and AXS-12, which are being developed for multiple indications. The Axsome Pain and Primary Care business unit ("Axsome PPC") houses Axsome's pain and primary care assets, including AXS-02 and AXS-06, and intellectual property which covers these and related product candidates and molecules being developed by Axsome and others. The Company aims to become a fully integrated biopharmaceutical company that develops and commercializes differentiated therapies that expand the treatment options available to caregivers and improve the lives of patients living with CNS disorders. The Company was incorporated on January 12, 2012 in the State of Delaware and now has operations in the United States and Australia.

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP") and include all adjustments necessary for the fair presentation of the Company's financial position for the periods presented. The consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. All material intercompany accounts and transactions have been eliminated during the consolidation process.

Amendment to Certificate of Incorporation

In connection with the completion of the Company's initial public offering ("IPO") on November 24, 2015, the Company's stockholders approved an amended and restated Certificate of Incorporation, in which its authorized capital stock consists of 150,000,000 shares of common stock, par value $0.0001 per share, and 10,000,000 shares of preferred stock, par value $0.0001 per share.

Liquidity and Capital Resources

The Company has incurred operating losses since its inception, and expects to continue to incur operating losses for the foreseeable future and may never become profitable. As of December 31, 2018, the Company had an accumulated deficit of $107.6 million.

In November 2015, the Company completed its IPO, whereby it sold 5,666,667 shares of common stock at a public offering price of $9.00 per share. The Company received gross proceeds of approximately $51.0 million and net proceeds of approximately $45.5 million, after deducting underwriting discounts and commissions and offering-related transaction costs.

In November 2016, the Company entered into a loan and security agreement with Silicon Valley Bank ("SVB") for a term loan of up to $20.0 million. The initial tranche of $10.0 million was funded shortly after executing the loan agreement. The Company did not achieve the conditional criteria to access the second and third tranches before the specified dates and the $10.0 million in additional term loan advances subsequently expired. In November 2018, the Company amended the loan and security agreement with SVB to provide an additional $4.0 million growth capital loan, related to the Company's narcolepsy clinical program with AXS-12. The additional capital was available to be drawn, at the Company's option, subject to the achievement of a specified clinical milestone. The Company's obligations under the loan and security agreement, as amended, along with the ability of the Company to draw down on the additional $4.0 million tranche, were subsequently extinguished in connection with the establishment of a new term loan facility with SVB during March 2019 (see below).

In March 2017, the Company completed an underwritten public offering, whereby it sold 4,304,813 shares of common stock at a public offering price of $3.74 per share. The Company received gross proceeds of approximately $16.1 million and net proceeds of approximately $14.8 million, net of underwriting discounts and offering expenses.

In October 2017, the Company entered into a sales agreement (the “Sales Agreement”) with Leerink Partners LLC ("Leerink"), pursuant to which the Company could sell up to $30 million in shares of its common stock from time to time through Leerink, acting as its sales agent, in one or more at-the-market offerings. The Company received approximately $4.2 million in gross proceeds, of which net proceeds were approximately $4.1 million from the sales of its common stock to Leerink under the Sales Agreement during the year ended December 31, 2018. In January 2019, the Company raised approximately $25.8 million in gross proceeds through the sale of 3,164,015 shares under the Sales Agreement. Upon completion of the final sale, the Sales Agreement was automatically terminated, Leerink received a commission of 3.0% of the gross proceeds for all shares sold under the Sales Agreement.

In December 2017, the Company completed a registered direct offering (“the 2017 Registered Direct Offering”) priced at the market, whereby it sold 1,783,587 shares of common stock and warrants to purchase up to an aggregate of 1,783,587 shares of its common stock at a combined purchase price of $5.325 per share. The Company received gross proceeds of approximately $9.5 million and net proceeds of approximately $8.8 million, net of underwriting discounts and offering expenses.

On September 27, 2018, the Company entered into a purchase agreement with certain institutional and accredited investors (collectively, the “RDO Investors”) for the sale by the Company directly to the RDO Investors of an aggregate of 2,966,667 shares of the Company’s common stock, at a purchase price of $3.00 per share (the “2018 Registered Direct Offering”), for gross proceeds of approximately $8.9 million. The 2018 Registered Direct Offering closed on October 1, 2018, and the Company received net proceeds of approximately $8.8 million, after deducting transaction expenses. The 2,966,667 shares of common stock sold in the 2018 Registered Direct Offering were offered and sold by the Company directly to the RDO Investors, without a placement agent, underwriter, broker or dealer, pursuant to a prospectus supplement to the 2016 Shelf Registration Statement.

In March 2019, the Company entered into a $24.0 million growth capital term loan facility with SVB and WestRiver. The two-tranche loan agreement consists of an initial $20.0 million tranche, which was funded shortly upon closing, with the remaining $4.0 million available to be drawn, at the Company’s option, subject to the achievement of positive data, on or prior to August 15, 2019, with respect to the Company’s ongoing Phase 2 clinical trial for AXS-12 in narcolepsy, sufficient to submit a Phase 3 protocol to FDA, provided that the Company has not received any objections from the FDA within thirty days after submission of such Phase 3 protocol. A portion of the first tranche was used to satisfy the Company’s existing obligations under its previously disclosed term loan facility with SVB, as amended, and such obligations are considered fully repaid and extinguished (refer to Note 6, Loan and Security Agreement).

The Company’s primary sources of cash have been proceeds from the issuance and sale of its common stock in public offerings. The Company has not yet commercialized any of its product candidates and cannot be sure if it will ever be able to do so. Even if the Company commercializes one or more of its product candidates, it may not become profitable. The Company’s ability to achieve profitability depends on a number of factors, including its ability to obtain regulatory approval for its product candidates, successfully complete any post-approval regulatory obligations and successfully commercialize its product candidates alone or in partnership. The Company may continue to incur substantial operating losses even if it begins to generate revenues from its product candidates.

The Company believes its existing cash will be sufficient to fund its anticipated operating cash requirements for at least twelve months following the date of this filing. The actual amount of cash that the Company will need to operate is subject to many factors, including, but not limited to, the timing, design and conduct of clinical trials for its product candidates. The Company is dependent upon significant future financing to provide the cash necessary to execute its current operations, including the commercialization of any of its product candidates.

The Company’s common stock is listed on the Nasdaq Global Market and trades under the symbol “AXSM”.

Note 2. Summary of Significant Accounting Policies

Significant Risks and Uncertainties

The Company's operations are subject to a number of factors that can affect its operating results and financial condition. Such factors include, but are not limited to: the results of clinical testing and trial activities of the Company's product candidates; the Company's ability to obtain regulatory approval to market its products, if approved; competition from products manufactured and sold or being developed by other companies; the price of, and demand for, Company products, if approved; the Company's ability to negotiate favorable licensing or other manufacturing and marketing agreements for its products, if approved; and the Company's ability to raise additional financing. If the Company does not successfully commercialize any of its product candidates, it will be unable to generate recurring product revenue or achieve and maintain profitability.

Use of Estimates

Management considers many factors in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. In preparing these financial statements, management used significant estimates in the following areas, among others: stock-based compensation expense; the determination of the fair value of the warrants; the accounting for research and development costs; and the recoverability of the Company's net deferred tax assets and related valuation allowance.

Foreign Currency Translation

Expenses denominated in foreign currency are translated into U.S. dollars at the exchange rate on the date the expense is incurred. Assets and liabilities of foreign operations are translated at period-end exchange rates. The effect of exchange rate fluctuations on translating foreign currency into U.S. dollars is included in the Statements of Operations and is not material to the Company's financial statements.

Segment and Geographic Information

Operating segments are defined as components of an enterprise for which separate discrete information is available for evaluation by the chief operating decision maker or decision making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business as one operating segment, which is the business of developing novel therapies for the management of CNS disorders.

Cash Equivalents

The Company considers all highly liquid investments that have maturities of three months or less when acquired to be cash equivalents. Cash equivalents are valued at cost, which approximates their fair value. There were no cash equivalents at December 31, 2018 and 2017.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash. The Company maintains its cash at financial institutions, which at times, exceed federally insured limits. At December 31, 2018, the majority of the Company's cash was held by one financial institution and the amount on deposit was in excess of Federal Deposit Insurance Corporation insurance limits. The Company has not recognized any losses from credit risks on such accounts since inception. The Company believes it is not exposed to significant credit risk on cash.

Fair Value of Financial Instruments

Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants at the measurement date. Assets and liabilities that are measured at fair value are reported using a three-level fair value hierarchy that prioritizes the inputs used to measure fair value. This hierarchy maximizes the use of observable inputs and minimizes the use of unobservable inputs. The three levels of inputs used to measure fair value are as follows:

Level 1—Quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Inputs other than quoted prices in active markets that are observable for the asset or liability, either directly or indirectly.

Level 3—Inputs that are unobservable for the asset or liability.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying amounts reported in the accompanying consolidated financial statements for accounts payable and accrued expenses approximate their respective fair values due to their short-term maturities. The fair value of the warrants are discussed in Note 3, "Fair Value Measurements."

Debt Issuance Costs

The Company incurred third-party costs in connection with the Company's term loans as described in Note 6 – Loan and Security Agreement. These costs are classified on the consolidated balance sheet as a direct deduction from the debt liability. The Company amortizes these costs over the term of its debt agreements as interest expense in the consolidated statement of operations.

Equipment

Equipment consists primarily of computer equipment and is recorded at cost. Equipment is depreciated on a straight-line basis over its estimated useful life, which the Company estimates to be three years. When equipment is sold or otherwise disposed of, the cost and related accumulated depreciation are removed from the accounts and the resulting gain or loss is included in operating expenses.

Research and Development Costs

Research and development expenses primarily consist of costs incurred in performing research and development activities, including preclinical studies, clinical trials, manufacturing costs, employee salaries and benefits, stock-based compensation expense, contract services, including external research and development expenses incurred under arrangements with third parties, such as contract research organizations ("CROs"), facilities costs, overhead costs, depreciation, and other related costs.

Generally, research and development costs are expensed as incurred. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and amortized over the period that the goods are delivered or the related services are performed, subject to an assessment of recoverability. The Company makes estimates of costs incurred in relation to external CROs, and clinical site costs. The Company analyzes the progress of clinical trials, including levels of patient enrollment, invoices received and contracted costs when evaluating the adequacy of the amount expensed and the related prepaid asset and accrued liability. Significant judgments and estimates must be made and used in determining the accrued balance and expense in any accounting period. The Company reviews and accrues CRO expenses and clinical trial study expenses based on work performed and relies upon estimates of those costs applicable to the stage of completion of a study. Accrued CRO costs are subject to revisions as such trials progress to completion. Revisions are charged to expense in the period in which the facts that give rise to the revision become known. With respect to clinical site costs, the financial terms of these agreements are subject to negotiation and vary from contract to contract. Payments under these contracts may be uneven, and depend on factors such as the achievement of certain events, the successful recruitment of patients, the completion of portions of the clinical trial or similar conditions. The objective of our policy is to match the recording of expenses in our financial statements to the actual services received and efforts expended. As such, expense accruals related to clinical site costs are recognized based on our estimate of the degree of completion of the event or events specified in the specific clinical study or trial contract.

Income Taxes

Income taxes are accounted for under the asset and liability method. Under this method, deferred tax assets and liabilities are recognized for the future tax consequences attributable to the differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases, operating losses, and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period that includes the enactment date. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company recognizes the tax benefit from an uncertain tax position only if it is more likely than not to be sustained upon examination based on the technical merits of the position as well as consideration of the available facts and circumstances. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. As of December 31, 2018, the Company does not believe any material uncertain tax positions are present. In the event the Company determines that accrual of interest or penalties are necessary in the future, the amount will be presented as a component of income tax expense.

Stock-Based Compensation

For stock options issued, the Company estimates the grant date fair value of each option using the Black-Scholes option pricing model. The Black-Scholes model takes into account the expected volatility of the Company’s common stock, the risk-free interest rate, the estimated life of the option, the closing market price of the Company’s common stock and the exercise price. The estimates utilized in the Black-Scholes calculation involve inherent uncertainties and the application of management judgment. In addition, the Company recognizes expense for equity award forfeitures as they occur. For awards subject to service-based vesting conditions, the Company recognizes stock-based compensation expense on a straight-line basis over the requisite service period, which is generally the vesting term. For awards subject to performance-based vesting conditions, the Company recognizes stock-based compensation expense using the accelerated attribution method when it is probable that the performance condition will be achieved. The expense related to the stock-based compensation is recorded within the financial statement line item the grantee’s cash compensation is recorded in.

The Company’s policy upon exercise of stock options is that shares will be issued as new shares drawing on the Company’s 2015 Omnibus Incentive Compensation Plan share pool that was adopted by the stockholders in November 2015.

Tax Credit

The tax credit represents the receipt of the New York City Biotechnology Tax Credit ("NYC Biotech credit"), and receipt by Axsome Therapeutics Australia PTY, LTD, the Company's Australian subsidiary, of the Australia Tax Incentive Credit, related to the Company's research and development expenses incurred for its product candidates. These expenses were incurred in prior periods and therefore the grant income was recorded when the funds were received.

Basic and Diluted Net Loss per Common Share

Basic net loss per share of common stock is computed by dividing net loss by the weighted average number of shares of common stock outstanding during the period. Diluted net loss per share of common stock includes the effect, if any, from the potential exercise or conversion of securities, such as convertible notes, warrants, and stock options, which would result in the issuance of incremental shares of common stock. As the impact of these items is anti-dilutive during periods of net loss, there was no difference between basic and diluted net loss per share of common stock for the years ended December 31, 2018, 2017, and 2016.

Recent Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2016-02, *Leases (Topic 842)*, which supersedes FASB Topic 840, *Leases (Topic 840)*, requires that assets and liabilities arising under leases be recognized on the balance sheet as well as additional quantitative and qualitative disclosures that provide the amount, timing, and uncertainty of cash flows related to lease agreements. In July 2018, the FASB also issued ASU No. 2018-11, *Leases (Topic 842)*, which provides (1) optional transition method that entities can use when adopting the standard and (2) a practical expedient that permits lessors to not separate nonlease components from the associated lease component if certain conditions are met. The standard is effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted upon issuance. The Company elected to use the transition method approved by the FASB in accordance with ASU No. 2018-11, *Leases*, which allows companies to apply the provisions of the new leasing standard as of January 1, 2019, without adjusting the comparative periods presented by recognizing a cumulative-effect adjustment to the opening balance of retained earnings. The Company applied a policy election to exclude short-term leases from balance sheet recognition and also elected certain practical expedients at adoption. As permitted under these expedients, the Company did not reassess whether existing contracts are or contain leases, the lease classification for any existing leases, initial direct costs for any existing lease and whether existing land easements and rights of way, that were not previously accounted for as leases, are or contain a lease. Although the Company is still finalizing its evaluation of the standard update and the quantification of its impact, the Company expects its adoption will not have a material impact its financial statements.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows (Topic 230) – Classification of Certain Cash Receipts and Cash Payments*, which is guidance to address diversity in practice with respect to how certain cash receipts and cash payments are presented and classified in the statement of cash flows. The updated guidance addresses eight specific cash flow issues with the objective of reducing the existing diversity that occurs in practice. The guidance is effective for annual and interim periods beginning after December 15, 2017. The Company has adopted this guidance effective January 1, 2018 and the adoption of the guidance did not have a material impact on the Company's financial statements.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation-Stock Compensation (Topic 718): Scope of Modification Accounting*. ASU 2017-09 provides clarity and reduces both (1) diversity in practice and (2) cost and complexity when applying the guidance in Topic 718, to a change to the terms or conditions of a share-based payment award. The amendments in ASU 2017-09 should be applied prospectively to an award modified on or after the adoption date. This ASU is effective for fiscal years beginning after December 15, 2017, including interim periods within those years. The Company has adopted this guidance effective January 1, 2018 and the adoption of the guidance did not have a material impact on the Company's financial statements.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting*, to simplify the accounting for share-based payments to nonemployees by aligning it with the accounting for share-based payments to employees, with certain exceptions. The standard will be effective for annual and interim periods beginning after December 15, 2018. The Company early adopted this guidance effective October 1, 2018 and the adoption did not have a material impact on the Company's financial statements.

In July 2018, the FASB issued ASU No. 2018-09, *Codification Improvements*, which provides technical corrections, clarifications, and other improvements to several topics in the FASB Accounting Standard Codification. The transition and effective date guidance is based on the facts and circumstances of each amendment. Some of the amendments do not require transition guidance and were effective upon issuance of the ASU. Amendments that do not have transition guidance are effective for annual periods beginning after December 15, 2018. The Company is currently evaluating the potential impact of the new guidance.

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*, which modifies, removes and adds certain disclosure requirements on fair value measurements based on the FASB Concepts Statement, Conceptual Framework for Financial Reporting-Chapter 8: Notes to the Financial Statements. The amendments on changes in unrealized gains and losses, the range and weighted average of significant unobservable inputs used to develop Level 3 fair value measurements and the narrative description of measurement uncertainty should be applied prospectively for only the most recent interim or annual period presented in the initial fiscal year of adoption. All other amendments should be applied retrospectively to all periods presented upon their effective date. The ASU is effective for fiscal years beginning after December 15, 2019, including interim periods within those years. The Company is currently evaluating the potential impact of the new guidance.

In August 2018, the SEC adopted the final rule under SEC Release No. 33-10532, *Disclosure Update and Simplification*, amending certain disclosure requirements that were redundant, duplicative, overlapping, outdated or superseded. The changes are generally expected to reduce or eliminate certain disclosures; however, the amendments did expand interim period disclosure requirements related to changes in stockholders' equity. The final rule was effective on November 5, 2018 and the adoption of the guidance did not have a material impact on the Company's financial statements.

Note 3. Fair Value Measurements

In accordance with *Accounting Standards Codification ("ASC") 820, Fair Value Measurements and Disclosures*, financial instruments were measured at fair value using a three-level hierarchy which maximizes use of observable inputs and minimizes use of unobservable inputs:

Level 1—Quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Inputs other than quoted prices in active markets that are observable for the asset or liability, either directly or indirectly.

Level 3—Inputs that are unobservable for the asset or liability.

2017 Warrants associated with Registered Direct Offering

In connection with the Company's 2017 Registered Direct Offering, the Company issued common stock warrants ("Common Warrants") to certain investors to purchase an aggregate of 1,783,587 shares of its common stock. The Common Warrants were exercisable at $5.25 per share and expired on December 11, 2018. Additionally, as part of the 2017 Registered Direct Offering, the Company issued warrants (the "Placement Agent Warrants') to certain investors affiliated with H.C. Wainwright & Co., LLC, the placement agent in the 2017 Registered Direct Offering to purchase an aggregate of 107,015 shares of its common stock. The Placement Agent Warrants were exercisable at $6.6562 and expired on December 11, 2018. The Common Warrants and Placement Agent Warrants (collectively the "2017 Warrants") were analyzed and it was determined that they required liability treatment. Under ASC 815 *Derivatives and Hedging* ("ASC 815"), registered common stock warrants that require the issuance of registered shares upon exercise and do not expressly preclude an implied right to cash settlement are accounted for as derivative liabilities. The Company classified these derivative warrant liabilities on the consolidated balance sheet as a current liability.

The fair value of the Common Warrants at December 4, 2017, the date these warrants were issued, and December 31, 2017 were determined to be approximately $2,064,000 and $2,683,000, respectively, as calculated using Black-Scholes with the following assumptions: (1) stock price of $5.00 and $5.60, respectively; (2) a risk-free rate of 1.66% and 1.76%, respectively; and (3) an expected volatility of 61% and 62%, respectively. The fair value of the Common Warrants were reported as a warrant liability on the balance sheet and the change in the fair value between December 4, 2017 and December 31, 2017 is reported as a change in fair value of the warrant liability on the statement of operations.

The fair value of the Placement Agent Warrants at December 4, 2017, the date these warrants were issued, and December 31, 2017 were determined to be approximately $81,000 and $108,000, respectively, as calculated using Black-Scholes with the following assumptions: (1) stock price of $5.00 and $5.60, respectively; (2) a risk-free rate of 1.66% and 1.76%, respectively; and (3) an expected volatility of 61% and 62%, respectively. The fair value of the Placement Agent Warrants were reported as a warrant liability on the balance sheet and the change in the fair value between December 4, 2017 and December 31, 2017 is reported as a change in fair value of the warrant liability on the statement of operations.

Level 3 Fair Value Sensitivity

Warrant liability

As of December 31, 2017, the fair value of the warrant liability utilizes inputs including: share price, expected volatility and risk-free rate.

- A 10% plus/minus change in share price will result in an estimated increase/decrease of $0.7 million in the value of the warrant liability,
- A 10% plus/minus change in the expected volatility will result in an estimated increase/decrease of $0.2 million in the value of the warrant liability, and
- A 10% plus/minus change in the risk-free interest rate will result in an immaterial change in the value of the warrant liability.

The 2017 Warrants associated with 2017 Registered Direct Offering expired on December 11, 2018, and therefore, the warrant liability was zero as of December 31, 2018.

There were no financial liabilities measured at fair value on a recurring basis as of December 31, 2016.

The following table sets forth a summary of changes in the fair value of Level 3 liabilities for the years ended December 31, 2018 and 2017:

December 31, 2018	Beginning of period	Issuances	Change in fair value (1)	End of period
Warrant liability	$ 2,791,000	$ —	$ (2,791,000)	$ —
Total	$ 2,791,000	$ —	$ (2,791,000)	$ —

December 31, 2017	Beginning of period	Issuances	Change in fair value (1)	End of period
Warrant liability	$ —	$ 2,145,000	$ 646,000	$ 2,791,000
Total	$ —	$ 2,145,000	$ 646,000	$ 2,791,000

(1) The change in the fair values of the warrants are recorded in the statements of operations.

Note 4. Net Loss per Common Share

The following table sets forth the computation of basic and diluted net loss per common share:

	Year ended December 31,		
	2018	2017	2016
Basic and diluted net loss per common share:			
Net loss	$ (30,965,464)	$ (28,943,392)	$ (27,201,653)
Weighted average common shares outstanding—basic and diluted	26,883,656	22,764,606	19,150,690
Net loss per common share—basic and diluted	$ (1.15)	$ (1.27)	$ (1.42)

The following potentially dilutive securities outstanding at December 31, 2018, 2017, and 2016 have been excluded from the computation of diluted weighted average shares outstanding, as they would be anti-dilutive:

	December 31,		
	2018	2017	2016
Stock options	2,291,163	2,315,638	1,772,050
Warrants	123,037	2,099,199	337,746
Total	2,414,200	4,414,837	2,109,796

Note 5. Accrued Expenses and Other Current Liabilities

At December 31, 2018 and 2017, accrued expenses consisted of the following:

	December 31,	
	2018	2017
Research and development	$ 2,266,285	$ 1,642,154
Accrued compensation	1,051,401	704,556
Other	525,613	332,824
Total	$ 3,843,299	$ 2,679,534

Note 6. Loan and Security Agreement

In November 2016, the Company entered into a $20.0 million Term Loan Agreement ("Original Term Loan") with SVB. The three-tranche Term Loan consists of an initial $10.0 million tranche triggered upon closing, with the remaining $10.0 million available to be drawn in two $5.0 million tranches, at the Company's option, subject to the achievement of certain clinical and financial milestones.

The Original Term Loan bore interest at an annual rate equal to 4.50% plus the prime rate, which is the greater of 3.50% or the Wall Street Journal prime rate, and was payable monthly. It was set to mature in November 2020 and had an interest-only payment period until December 1, 2017, which could be extended to May 2018 upon the drawing of the second tranche. Following the interest only payment period, the Company began making monthly payments of principal and interest which were to continue until the maturity date. Principal payments coming due within twelve months have been classified as current liabilities in the accompanying balance sheet. In addition, the Company was required to pay a final payment fee of 8.5% of the principal amount extended on the date of repayment of the Term Loan, which was being accreted and amortized into interest expense using the effective interest rate method over the term of the loan. Because the Company did not achieve the conditional criteria to access the second and third term advances before the specified dates, the $10.0 million in additional term loan advances expired and the Company began to repay principal in December 2017.

The Company was permitted to prepay all, but not less than all, of the Original Term Loan subject to a prepayment premium of 3.0% of the outstanding principal if prepaid within two years of the effective date of the loan, 2.0% of the outstanding principal if prepaid during the third year of the loan, and 1.0% of the outstanding principal if prepaid after the third year. The Term Loan was collateralized by a security interest in all of the Company's assets except intellectual property. The Company's intellectual property was subject to a negative pledge.

In November 2018, the Company amended the existing term loan facility to provide an additional $4.0 million growth capital loan, related to Axsome's narcolepsy clinical program with AXS-12 ("First Amendment to the Loan and Security Agreement"). This additional capital was available to be drawn, at Axsome's option, subject to the achievement of positive results from the Company's upcoming Phase 2 trial of AXS-12 in narcolepsy sufficient to proceed to a Phase 3 trial. The financial terms for this additional growth capital were more favorable than those of the original term loan. All other terms and conditions from the original term loan agreement remain in place. The additional $4.0 million growth capital loan had to be drawn by May 31, 2019 and would bear interest at an annual rate equal to the greater of the prime rate plus 2.00%, or 7.25%, if drawn.

The Company evaluated whether the First Amendment to the Loan and Security Agreement entered into in November 2018 represented a debt modification or extinguishment in accordance with ASC 470-50, *Debt - Modifications and Extinguishments*. Upon determining that the change in cash flows between the previous and current loans was not greater than 10%, the Company accounted for the transaction as a debt modification. Since the borrowing capacity of the First Amendment to the Loan and Security Agreement is greater than the borrowing capacity from the Original Term Loan agreement, the unamortized deferred costs, any fees paid to the lender, and any third-party costs incurred are deferred and amortized over the term of the First Amendment. As of November 2018, the unamortized balance of debt discount costs incurred in connection with the Original Term Loan and additional debt discount costs incurred in connection with entry into the First Amendment of the Loan and Security Agreement, were being amortized through maturity in November 2020 utilizing the effective interest rate method and straight-line method, respectively.

The book value of debt approximates its fair value given its short term maturity and variable interest rate. Interest expense was $751,670 and $869,678 and amortization of the final payment was $266,668 and $346,978 for the years ended December 31, 2018 and 2017, respectively.

Long-term debt and unamortized debt discount balances are as follows:

	December 31, 2018	December 31, 2017
Outstanding principal amount	$ 6,388,889	$ 9,722,222
Debt discount, net of current portion	563,864	274,116
Long-term debt, net of debt discount	6,952,753	9,996,338
Less current portion of principal	(3,333,333)	(3,333,333)
Loan payable, long-term	$ 3,619,420	$ 6,663,005
Current portion of outstanding principal amount	3,333,333	3,333,333
Current portion of debt discount	(41,939)	(63,987)
Loan payable, current portion	$ 3,291,394	$ 3,269,346

In connection with the Original Term Loan, SVB and Life Science Loans, LLC received warrants to purchase an aggregate 65,228 shares of the Company's common stock at an exercise price of $7.41 per share, which are exercisable for seven years from the date of issuance.

The proceeds of $10.0 million were allocated based on the relative fair values of the debt instrument and the warrant instrument. The fair value of the warrants and the closing costs were recorded as debt discounts and were being amortized using the effective interest rate method over the term of the loan. Amortization of the debt discount was $106,308 and $123,543 for the years ended December 31, 2018 and 2017, respectively.

In connection with the First Amendment to the Loan and Security Agreement, SVB and WestRiver Innovation Lending Fund VIII, L.P. received warrants to purchase an aggregate 15,750 shares of the Company's common stock at an exercise price of $3.06 per share, which are exercisable for seven years from the date of issuance. Altogether, the Company issued 63,000 shares of common stock concurrent with the signing of this amendment, of which 15,750 were earned immediately. The warrants to purchase the remaining 47,250 shares of common stock would be earned upon the funding. Amortization of the debt discount was $2,659 for the year ended December 31, 2018.

Scheduled Principal Payments on Outstanding Debt, as of December 31, 2018, are as follows:

2019	$ 3,333,333
2020	3,055,556
Total principal payments outstanding	$ 6,388,889

In March 2019, the Company established a new term loan facility with SVB and WestRiver in the aggregate principal amount of up to $24.0 million. The Company's obligations under November 2016 loan and security agreement, as amended, along with the ability of the Company to draw down on the additional $4.0 million tranche, were subsequently extinguished in connection with the establishment of the new term loan facility during March 2019 (see Note 14 – Subsequent Events).

Note 7. Stockholders' Equity

Capital Structure

As of December 31, 2014, the Company was authorized to issue 14,689,000 shares of common stock at $0.0001 par value per share. In April 2015, the Company's board of directors and stockholders approved an increase of the Company's authorized shares of common stock to 22,033,500 shares. In connection with the close of the Company's IPO on November 24, 2015, the Company's stockholders approved an amended and restated certificate of incorporation increasing the number of authorized shares of common stock to 150,000,000 and the number of authorized shares of preferred stock to 10,000,000, par value $0.0001 per share.

In November 2015, the Company completed its IPO, whereby it sold 5,666,667 shares of common stock at a public offering price of $9.00 per share. The Company received gross proceeds of approximately $51.0 million and net proceeds of approximately $45.5 million, after deducting underwriting discounts and commissions and offering-related transaction costs.

In March 2017, the Company completed an underwritten public offering, whereby it sold 4,304,813 shares of common stock at a public offering price of $3.74 per share. The Company received gross proceeds of approximately $16.1 million and net proceeds of approximately $14.8 million, net of underwriting discounts and offering expenses.

In October 2017, the Company entered into the Sales Agreement with Leerink , pursuant to which the Company may sell up to $30 million in shares of its common stock from time to time through Leerink, acting as its sales agent, in one or more at-the-market offerings. The Company received approximately $4.2 million in gross proceeds, of which net proceeds were approximately $4.1 million from the sales of its common stock to Leerink under the Sales Agreement during the year ended December 31, 2018. In January 2019, the Company raised approximately $25.8 million in gross proceeds through the sale of 3,164,015 shares under the Sales Agreement. Upon completion of the final sale, the Sales Agreement was automatically terminated, Leerink received a commission of 3.0% of the gross proceeds for all shares sold under the Sales Agreement.

In December 2017, the Company completed the Registered Direct Offering, whereby it sold an aggregate of $9.5 million worth of units (“Units”) at a purchase price of $5.325 per Unit with each Unit consisting of (i) one share of the Company’s common stock, and (ii) a Common Warrant at an exercise price equal to $5.25 per share. The Company sold an aggregate of 1,783,587 Units for gross proceeds of approximately $9.5 million and net proceeds of approximately $8.8 million, net of underwriting discounts and offering expenses. Additionally, the Company issued 107,015 Placement Agent Warrants. The Company incurred issuance costs associated with the Units offering of $745,856, which included $81,000 related to issuance of 107,015 Placement Agent Warrants, of which, $583,768 was allocated to the common stock sold and was recorded as a reduction to equity. The remaining amount was allocated to the Common Warrants and was expensed. The Placement Agent Warrants have the same terms as the Common Warrants, except for the exercise price of $6.6562 per share. The Common Warrants priced at $5.25 and Placement Agent Warrants priced at $6.6562 utilized the 2016 Shelf Registration Statement for a total of $9.4 million and $712,313.

On September 27, 2018, the Company entered into a purchase agreement with certain institutional and accredited investors (collectively, the “RDO Investors”) for the sale by the Company directly to the RDO Investors of an aggregate of 2,966,667 shares of the Company’s common stock, at a purchase price of $3.00 per share (the “2018 Registered Direct Offering”), for gross proceeds of approximately $8.9 million. The 2018 Registered Direct Offering closed on October 1, 2018, and the Company received net proceeds of approximately $8.8 million, after deducting transaction expenses. The 2,966,667 shares of common stock sold in the 2018 Registered Direct Offering were offered and sold by the Company directly to the RDO Investors, without a placement agent, underwriter, broker or dealer, pursuant to a prospectus supplement to the 2016 Shelf Registration Statement.

The holders of shares of common stock are entitled to one vote for each share of common stock held at all meetings of stockholders and written actions in lieu of meetings. The holders of shares of common stock are entitled to receive dividends, if and when declared by the board of directors.

Shelf Registration Statement

On December 1, 2016, the Company filed a shelf registration statement with the Securities and Exchange Commission (“SEC”) for the issuance of common stock, preferred stock, warrants, rights, debt securities and units up to an aggregate amount of $150.0 million, which the Company refers to as the 2016 Shelf Registration Statement. On December 16, 2016, the 2016 Shelf Registration Statement was declared effective by the SEC.

The 2016 Shelf Registration Statement is currently our only active shelf registration. After deducting shares already sold, there is approximately $77.5 million of common stock that remains available for sale under the 2016 Shelf Registration as of the date of this filing. In the future, the Company may also periodically offer one or more of these securities in amounts, prices and terms to be announced when and if the securities are offered. At the time any of the securities covered by the 2016 Shelf Registration Statement are offered for sale, a prospectus supplement will be prepared and filed with the SEC containing specific information about the terms of any such offering.

Equity Incentive Plans

The Company had granted stock options under its 2013 Equity Compensation Plan (the "2013 Plan"), which was adopted for employees and consultants for the purpose of advancing the interests of the Company's stockholders by enhancing its ability to attract, retain and motivate persons who are expected to make important contributions to the Company. In November 2015, the 2015 Omnibus Incentive Compensation Plan (the "2015 Plan") was adopted by the Company's stockholders. The 2015 Plan is the successor to the Company's 2013 Plan. In conjunction with the adoption of the 2015 Plan, no additional grants were made from the 2013 Plan and options from the 2013 Plan remain outstanding. As of December 31, 2018, there were 3,609,552 shares available for future grant under the 2015 Plan.

Stock Options

The following table summarizes stock option activity as of December 31, 2018:

	Number of shares	Weighted average exercise price	Weighted average contractual term	Aggregate intrinsic value
Outstanding at December 31, 2017	2,315,638	$ 5.57		
Granted	816,723	3.12		
Exercised	(278,925)	1.36		
Forfeited	(325,835)	5.79		
Expired	(236,438)	6.70		
Outstanding at December 31, 2018	2,291,163	$ 5.06	7.8	$ 216,649
Vested and expected to vest at December 31, 2018	2,265,994	$ 5.09	7.7	$ 195,112
Exercisable at December 31, 2018	1,317,299	$ 5.37	6.8	$ 191,115

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option pricing model. The expected term of the Company's stock options has been determined utilizing the "simplified" method as described in the SEC's Staff Accounting Bulletin No. 107 relating to stock-based compensation. The simplified method was chosen because the Company has limited historical option exercise experience due to its short operating history. The risk-free interest rate is based on the U.S. Treasury yield in effect at the time of grant for a period approximately equal to the expected term of the award. 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. Expected volatility is based on historical volatilities of similar entities within the Company's industry which were commensurate with the Company's expected term assumption. The relevant data used to determine the value of the stock option grants for the years ended December 31, 2018, 2017, and 2016 is as follows:

Black-Scholes option valuation assumptions	2018	2017	2016
Risk-free interest rates	2.0 - 3.1 %	1.6 - 2.2 %	0.9 - 2.0 %
Dividend yield	—	—	—
Volatility	74 - 87 %	73 - 77 %	69 - 75 %
Weighted average expected term	3.66 - 6.13 years	3.50 - 6.12 years	3.25 - 6.25 years

The weighted average grant date fair value of options granted was $1.99, $3.06, and $5.13 per option for the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, there was $2.7 million of total unrecognized compensation cost related to non-vested stock options which is expected to be recognized over a weighted average period of 2.3 years. These amounts do not include 38,024 options outstanding as of December 31, 2018, which are performance-based and vest upon the achievement of certain corporate milestones. The total intrinsic value of options exercised (the difference in the market price of the Company's common stock on the exercise date and the price paid by the optionee to exercise the option) was approximately $0.5 million for the years ended December 31, 2018. Stock-based compensation will be measured and recorded if and when it is probable that the milestone will occur.

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

	2018	2017	2016
Research and development	$ 391,946	$ 613,629	$ 1,115,626
General and administrative	1,363,028	1,458,581	915,792
Total	$ 1,754,974	$ 2,072,210	$ 2,031,418

Performance-Based Awards

During the year ended December 31, 2018, the Company issued 19,000 performance-based awards at an exercise price of $2.18, to employees that vest upon completion of certain clinical events. During the year ended December 31, 2017, the Company issued 20,650 performance-based awards, with a weighted average exercise price of $5.70, to employees that vest upon completion of certain clinical events. For awards granted to employees with performance conditions, no expense will be recognized, and no measurement date can occur, until the occurrence of the event is probable. For awards granted to non-employees, the Company will recognize the lowest aggregate amount within the range of potential values as expense until the measurement date is established. For the years ended December 31, 2018, 2017, and 2016, the Company recognized $1,587, $59,424, and $604,866, respectively, as expense related to performance-based awards.

Note 8. Warrants

As of December 31, 2018, the Company had outstanding warrants to purchase 123,037 shares of common stock. The following table summarizes warrant activity as of December 31, 2018, 2017, and 2016:

	Warrants	Weighted average exercise price
Outstanding at December 31, 2015	272,518	$ 2.02
Issued	65,228	7.41
Outstanding at December 31, 2016	337,746	3.06
Issued	1,890,602	5.33
Exercised	(129,149)	1.30
Outstanding at December 31, 2017	2,099,199	5.21
Issued	15,750	3.06
Exercised	(101,310)	1.30
Expired	(1,890,602)	5.33
Outstanding at December 31, 2018	123,037	$ 6.35

On November 26, 2018, in connection with the First Amendment to the Loan and Security Agreement, SVB and WestRiver Innovation Lending Fund VIII, L.P. received warrants to purchase 15,750 shares of the Company's stock at an exercise price of $3.06 per share, which are exercisable for seven years from the date of issuance ("2018 warrants"). The warrants were classified as a component of stockholders' equity. The 2018 warrants have a seven year term and expire on November 25, 2025.

In connection with the Registered Direct Offering, which was completed on December 11, 2017, the Company issued Common Warrants and Placement Agent Warrants to purchase 1,783,587 shares and 107,015 shares of common stock, respectively, with an exercise price of $5.25 per share and $6.6562 per share, respectively, which are exercisable from the date of issuance until December 11, 2018 ("2017 warrants"). The Common Warrants and Placement Agent Warrants were classified as warrant liability. See Note 3, "Fair Value Measurements", for the fair value calculations of the warrant liability. The 2017 warrants had a 1 year term and expired on December 11, 2018.

In connection with the Company's debt financing which was completed on November 9, 2016, the Company issued warrants to purchase 65,228 shares of common stock with an exercise price of $7.41 per share, which are exercisable upon issuance ("2016 warrants"). The warrants were classified as a component of stockholders' equity. The 2016 warrants have a seven year term and expire on November 8, 2023.

On November 3, 2014, the Company issued warrants to purchase 42,059 shares of common stock with an exercise price of $5.94 per share to the placement agent in connection with the issuance of certain convertible notes from September 2014 through November 2014 (the "September 2014 Notes"), which were exercisable upon issuance ("2014 warrants"). The warrants were initially classified as a liability in the consolidated financial statements, as upon a qualified financing, the warrant price would automatically adjust to a 10% premium to the conversion price of the September 2014 Notes in such mandatory conversion. The initial fair value of the warrant liability was $79,129 which was recorded as a discount to the notes and amortized over the term of the original September 2014 Notes. Upon the note amendment that occurred in September 2015, the discount was included in the carrying amount in the calculation of a loss on extinguishment. In connection with the automatic conversion of the September 2014 Notes upon the close of the Company's IPO in November 2015, the warrant liability was reclassified to equity. The 2014 warrants have a five year term and expire on November 2, 2019.

On October 29, 2013, the Company issued warrants to purchase 230,459 shares of common stock with an exercise price of $1.30 per share to the placement agent in connection with the June 2013 Notes, which were exercisable upon issuance ("2013 warrants"). The warrants were classified as a component of stockholders' equity. The 2013 warrants had a five year term. 129,149 warrants and 101,310 warrants were exercised in 2017 and 2018, respectively.

The initial fair value of the warrants were estimated using the Black-Scholes option pricing model with the following assumptions:

Black-Scholes option valuation assumptions	2018 warrants	2017 warrants	2016 warrants	2014 warrants	2013 warrants
Risk-free interest rate	3.0 %	1.7 %	1.8 %	1.6 %	1.4 %
Dividend yield	—	—	—	—	—
Volatility	85 %	61 %	73 %	70 %	64 %
Weighted average contractual term	7 years	1 year	7 years	5 years	5 years

In connection with the Company's new term loan facility with SVB and WestRiver which was completed in March 2019, the Company issued warrants to purchase 70,000 shares of the Company's common stock at a price per share equal to $8.10. The warrants will be earned based upon the usage of the facility and are exercisable until March 4, 2026. The warrants were classified as a component of stockholders' equity.

Note 9. License Agreements

In 2012, the Company entered into three exclusive license agreements with Antecip Bioventures II LLC, or Antecip, an entity owned by Axsome's Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which it was granted exclusive licenses to develop, manufacture, and commercialize Antecip's patents and applications related to the development of AXS-02, AXS-05, and AXS-04, a product candidate that is currently in early stage development, anywhere in the world for veterinary and human therapeutic and diagnostic use. Pursuant to the agreements, the Company is required to use commercially reasonable efforts to develop, obtain regulatory approval for and commercialize AXS-02, AXS-05, and AXS-04. Under the terms of the agreements, the Company is required to pay to Antecip a royalty equal to 4.5% for AXS-02, 3.0% for AXS-05, and 1.5% for AXS-04, of net sales of products containing the licensed technology by the Company, its affiliates, or permitted sublicensees. These royalty payments are subject to reduction by an amount up to 50.0% of any required payments to third parties. Unless earlier terminated by a party for cause or by the Company for convenience, the agreements shall remain in effect on a product-by-product and country-by-country basis until the later to occur of (i) the applicable product is no longer covered by a valid claim in that country or (ii) 10 years from the first commercial sale of the applicable product in that country. Upon expiration of the agreements with respect to a product in a country, the Company's license grant for that product in that country will become a fully paid-up, royalty-free, perpetual non-exclusive license. If Antecip terminates any of the agreements for cause, or if the Company exercises its right to terminate any of the agreements for convenience, the rights granted to the Company under such terminated agreement will revert to Antecip. To date, the Company has not been required to make any payments to Antecip under any of the license agreements.

Note 10. Commitments and Contingencies

Operating Leases

The Company's offices are located in New York, New York. The Company is not currently under a lease agreement. Rent expense incurred during the years ended December 31, 2018, 2017 and 2016 was $315,301, $307,557, and $254,170.

Note 11. Income Taxes

As of December 31, 2018, the Company had U.S. federal net operating loss ("NOL") carryforwards of approximately $87 million. NOLs amounting to $60 million generated before the 2018 tax year will start expiring beginning 2033, and the NOL of approximately $27 million generated in 2018 has an indefinite carryforward period. The NOL carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. NOL carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders, as defined under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, as well as similar state tax provisions. This could limit the amount of NOLs that the Company can utilize annually to offset future taxable income or tax liabilities.

The components of the Company's deferred tax assets are as follows:

	December 31, 2018	December 31, 2017	December 31, 2016
Deferred tax assets:			
Net federal operating loss carryforward	$ 18,911,435	$ 12,844,032	$ 12,747,837
Net foreign operating loss carryforward	40,927	49,846	23,293
Net state operating loss carryforward	11,842,460	7,981,812	4,068,086
Non-cash compensation	1,625,560	1,719,315	1,450,620
Research and development credits	7,651,781	5,713,709	3,491,251
Deferred finance costs	38,578	44,042	—
Interest Expense	400,946	—	—
Charitable Contribution	5,408	—	—
Fixed Assets	8,595	2,597	—
Accrued expenses	732,958	472,004	308,007
Deferred tax asset, excluding valuation allowance	41,258,648	28,827,357	22,089,094
Fixed Assets	—	—	(19,985)
Less valuation allowance	(41,258,648)	(28,827,357)	(22,069,109)
Net deferred tax assets	$ —	$ —	$ —

The Company records a valuation allowance to reduce the deferred tax assets reported if, based on the weight of available evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a full valuation allowance against its deferred tax assets at December 31, 2018, 2017, and 2016 because the Company's management has determined that it is more likely than not that these assets will not be realized. Valuation allowance increased $12.5 million, $6.7 million, and $14.3 million, in 2018, 2017, and 2016, respectively, as a result of the increase of the deferred tax assets.

There was no income tax expense (benefit) recorded by the Company due to its net loss tax position and full valuation allowance during the years ended December 31, 2018, 2017, and 2016. A reconciliation of income tax expense (benefit) at the statutory federal income tax rate and income taxes as reflected in the consolidated financial statements is as follows:

	December 31, 2018	December 31, 2017	December 31, 2016
U.S. federal statutory income tax rate	21.0 %	34.0 %	34.0 %
State taxes, net of federal benefit	13.1	10.0	9.4
Permanent differences	(0.2)	(2.9)	(3.7)
Tax credit	6.3	7.7	12.8
US Federal tax rate change - tax reform	—	(25.4)	—
Change in valuation allowance	(40.2)	(23.4)	(52.5)
Effective tax rate	— %	— %	— %

The Company is not currently under examination at the federal or state levels and as of the date of the consolidated financial statements there were no known assessments. The Company's U.S. federal and state net operating losses have occurred since its inception in 2012 and as such, tax years subject to potential tax examination could apply from that date because the utilization of net operating losses from prior years opens the relevant year to audit by the IRS and/or state taxing authorities.

Impact of U.S. Tax Reform

On December 22, 2017, the U.S. President signed the Tax Cuts and Jobs Act (the "Act") into law. Effective January 1, 2018, among other changes, the Act (1) reduces the Company's U.S. federal corporate tax rate from 34 percent to 21 percent, (2) changes the rules relating to net operating loss ("NOL") carryforwards and carrybacks, (3) eliminates the corporate alternative minimum tax ("AMT") and changes how existing AMT credits can be realized; and

(4) requires companies to pay a one-time transition tax on certain unrepatriated earnings of foreign subsidiaries. In addition, the Act makes the AMT credit refundable in tax years beginning after 2017.

The SEC staff issued Staff Accounting Bulletin ("SAB") 118, which provides guidance on accounting for the tax effects of the Tax Act. SAB 118 provides a measurement period that should not extend beyond one year from the Tax Act enactment date for companies to complete the accounting under Accounting Standards Codification (ASC) 740. In accordance with SAB 118, a company must reflect the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 is complete. To the extent that a company's accounting for certain income tax effects of the Tax Act is incomplete but it is able to determine a reasonable estimate, it must record a provisional estimate in the financial statements. If a company cannot determine a provisional estimate to be included in the financial statements, it should continue to apply ASC 740 on the basis of the provisions of the tax laws that were in effect immediately before the enactment of the Tax Act.

As of December 31, 2018, the Company completed its accounting for the tax effects of enactment of the Tax Act. The Tax Act did not have a material impact on the financial statements since the Company's deferred temporary differences in the United States are fully offset by a valuation allowance and the Company does not have any significant off shore earnings from which to record the mandatory transition tax.

Note 12. Related Party Transactions

From the Company's inception, Herriot Tabuteau, M.D. has been the Company's founder, Chief Executive Officer, Chairman of the Company's board of directors, and the beneficial owner of more than 5% of the outstanding shares of the Company's common stock. In connection with the formation of the Company, in January 2012, the Company issued to Antecip Capital LLC, an entity controlled by Dr. Tabuteau, an aggregate of 7,344,500 shares of the Company's common stock for nominal consideration.

The Company is a party to three exclusive license agreements with Antecip Bioventures II LLC, an entity owned by Dr. Tabuteau. See Note 9 for further information regarding the license agreements.

Note 13. Quarterly Consolidated Financial Data (Unaudited)

	2018			
	Mar. 31	June 30	Sept. 30	Dec. 31
Total operating expenses	$ 7,163,210	$ 7,989,593	$ 8,243,459	$ 9,450,315
Net loss	$ (4,805,559)	$ (8,280,916)	$ (8,281,974)	$ (9,597,015)
Net loss per common share, basic and diluted (1)	$ (0.19)	$ (0.32)	$ (0.31)	$ (0.32)

	2017			
	Mar. 31	June 30	Sept. 30	Dec. 31
Total operating expenses	$ 7,672,033	$ 6,750,738	$ 6,297,416	$ 6,444,120
Net loss	$ (7,995,039)	$ (7,084,316)	$ (6,433,536)	$ (7,430,501)
Net loss per common share, basic and diluted (1)	$ (0.41)	$ (0.30)	$ (0.27)	$ (0.31)

(1) Basic and diluted net loss per common share is computed independently for each of the quarters presented. Therefore, the sum of all quarterly basic and fully diluted net loss per common share may not equal the annual basic and diluted net loss per common share.

Note 14. Subsequent Events

In January 2019, the Company received approximately $25.8 million in gross proceeds, of which net proceeds were $25.0 million through the sale of 3,164,015 shares under the existing at-the-market facility with Leerink Partners LLC. Sales of the shares of common stock in the at-the-market offerings were made pursuant to a prospectus supplement to the 2016 Registration Statement.

In March 2019, the Company entered into a $24.0 million growth capital term loan facility with SVB and WestRiver. The two-tranche loan agreement consists of an initial $20.0 million tranche, which was funded shortly upon closing, with the remaining $4.0 million available to be drawn, at the Company's option, subject to the achievement of positive data, on or prior to August 15, 2019, with respect to the Company's ongoing Phase 2 clinical trial for AXS-12 in narcolepsy, sufficient to submit a Phase 3 protocol to FDA, provided that the Company has not received any objections from the FDA within thirty days after submission of such Phase 3 protocol. A portion of the first tranche was used to satisfy the Company's existing obligations under its previously disclosed term loan facility with SVB, as amended, and such obligations are considered fully repaid and extinguished (refer to Note 6, Loan and Security Agreement). The loan bears interest at an annual rate equal to the greater of (i) seven and one-half of one percent (7.50%) and (ii) two percent (2%) above the Prime Rate. The loan advances mature in February 2023 and have an interest-only payment period of 12 months, which may be extended to 18 months upon the drawing of the second tranche. In connection with the loan agreement, the Company issued warrants to purchase 70,000 shares of the Company's common stock at a price per share equal to $8.10. The warrants will be earned based upon the usage of the facility and are exercisable until March 4, 2026.

INDEX EXHIBITS

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation of the Company (Incorporated by reference, Exhibit 3.1 to the Company's Form 8-K (No. 001-37635) filed November 24, 2015.)
3.2	Amended and Restated Bylaws of the Company (Incorporated by reference, Exhibit 3.2 to the Company's Form 8-K (No. 001-37635) filed November 24, 2015.)
4.1	Specimen Certificate evidencing shares of Company's common stock (Incorporated by reference, Exhibit 4.1 to Amendment No. 1 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 30, 2015.)
4.2	Form of warrant to purchase shares of Company's common stock issued in 2013 (Incorporated by reference, Exhibit 4.2 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
4.3	Form of warrant to purchase shares of Company's common stock issued in 2014 (Incorporated by reference, Exhibit 4.3 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
4.4	Warrant Agreement between Axsome Therapeutics, Inc. and Silicon Valley Bank, dated November 9, 2016 (Incorporated by reference, Exhibit 4.1 to the Company's Current Report on Form 8-K filed November 10, 2016.)
4.5	Warrant Agreement between Axsome Therapeutics, Inc. and Life Sciences Loans, LLC, dated November 9, 2016 (Incorporated by reference, Exhibit 4.2 to the Company's Current Report on Form 8-K filed November 10, 2016.)
4.6	Form of Warrant (Incorporated by reference, Exhibit 4.1 to the Company's Current Report on Form 8-K filed December 4, 2017.)
4.7**	Form of Warrant, with respect to November 2018 First Amendment to Loan and Security Agreement.
4.8**	Form of Warrant, with respect to March 2019 Loan and Security Agreement.
10.1+	Axsome Therapeutics, Inc. 2013 Equity Compensation Plan and Form of Nonqualified Stock Option Agreement thereunder (Incorporated by reference, Exhibit 10.1 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
10.2+	Axsome Therapeutics, Inc. 2015 Omnibus Incentive Compensation Plan (Incorporated by reference, Exhibit 10.6 to Amendment to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 30, 2015.)
10.3+	Axsome Therapeutics, Inc. Form of Stock Option Agreement pursuant to the 2015 Omnibus Incentive Compensation Plan (Incorporated by reference, Exhibit 99.2 to the Company's Registration Statement on Form S-8 (No. 333-208579) filed December 16, 2015.)
10.4*	License Agreement, dated January 12, 2012, by and between the Company and Antecip Bioventures II LLC, as modified by the First Amendment to License Agreement, dated August 21, 2015, by and between the Company and Antecip Bioventures II LLC (Incorporated by reference, Exhibit 10.2 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
10.5*	License Agreement, dated April 17, 2012, by and between the Company and Antecip Bioventures II LLC, as modified by the First Amendment to License Agreement, dated August 21, 2015, by and between the Company and Antecip Bioventures II LLC (Incorporated by reference, Exhibit 10.3 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
10.6*	License Agreement, dated June 6, 2012, by and between the Company and Antecip Bioventures II LLC, as modified by the First Amendment to License Agreement, dated August 21, 2015, by and between the Company and Antecip Bioventures II LLC (Incorporated by reference, Exhibit 10.4 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
10.7+	Consulting Agreement, dated April 13, 2012, by and between the Company and Mark Coleman, M.D., as modified by the First Amendment to Consulting Agreement, dated June 2, 2014, by and between the Company and Mark Coleman, M.D (Incorporated by reference, Exhibit 10.5 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)

10.8	Loan and Security Agreement, dated as of November 9, 2016, by and between Axsome Therapeutics, Inc., and Silicon Valley Bank (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K filed November 10, 2016.)
10.9+	John Golubieski Offer Letter, dated July 5, 2017 (Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed August 9, 2017.)
10.10	Form of Purchase Agreement, dated as of November 30, 2017 among Axsome Therapeutics, Inc. and the purchasers thereunder (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K filed December 4, 2017.)
10.11+	Nick Pizzie Offer Letter, dated April 16, 2018 (Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed May 8, 2018.)
10.12	Form of Purchase Agreement, dated as of September 27, 2018, by and among the Company and the investors party thereto (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K, filed September 28, 2018.)
10.13**	First Amendment to Loan and Security Agreement, dated as of November 26, 2018, by and between the Company and Silicon Valley Bank.
10.14**	Loan and Security Agreement, dated as of March 5, 2019, by and among the Company, Silicon Valley Bank and WestRiver Innovation Lending Fund VIII, L.P.
21.1	Subsidiaries of the Company (Incorporated by reference, Exhibit 21.1 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
23.1	Consent of Ernst & Young LLP.
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a)/15d-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a)/15d-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification of Principal Executive Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (furnished herewith).
32.2	Certification of Principal Financial Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (furnished herewith).
101	Interactive data files pursuant to Rule 405 of Regulation S-T: (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations, (iii) Consolidated Statements of Cash Flows, and (iv) the Notes to Consolidated Financial Statements.

+ Indicates management contract or compensatory plan.

* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

* Filed herewith.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, on this 14th day of March 2019.

AXSOME THERAPEUTICS, INC.

By /s/ Herriot Tabuteau, M.D.
Herriot Tabuteau, M.D.
Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this report has been signed by the following persons on behalf of the registrant and in the capacities and on the dates indicated:

Signature	Title	Date
/s/ Herriot Tabuteau, M.D. Herriot Tabuteau, M.D.	Chief Executive Officer and Chairman of the Board (Principal Executive Officer)	March 14, 2019
/s/ Nick Pizzie Nick Pizzie	Chief Financial Officer (Principal Financial and Accounting Officer)	March 14, 2019
/s/ Roger Jeffs, Ph.D. Roger Jeffs, Ph.D.	Director	March 14, 2019
/s/ Mark Coleman, M.D. Mark Coleman, M.D.	Director	March 14, 2019
/s/ Mark Saad Mark Saad	Director	March 14, 2019
/s/ Myrtle Potter Myrtle Potter	Director	March 14, 2019

THIS WARRANT AND THE SHARES ISSUABLE HEREUNDER HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "**ACT**"), OR THE SECURITIES LAWS OF ANY STATE AND, EXCEPT AS SET FORTH IN SECTIONS 5.3 AND 5.4 BELOW, MAY NOT BE OFFERED, SOLD, PLEDGED OR OTHERWISE TRANSFERRED UNLESS AND UNTIL REGISTERED UNDER SAID ACT AND LAWS OR, IN THE OPINION OF LEGAL COUNSEL IN FORM AND SUBSTANCE SATISFACTORY TO THE ISSUER, SUCH OFFER, SALE, PLEDGE OR OTHER TRANSFER IS EXEMPT FROM SUCH REGISTRATION.

WARRANT TO PURCHASE STOCK

Company: Axsome Therapeutics, Inc., a Delaware corporation
Number of Shares: As set forth in Paragraph A below
Type/Series of Stock: Common Stock, $0.0001 par value per share
Warrant Price: $2.06 per Share, subject to adjustment
Issue Date: November 26, 2018
Expiration Date: November 25, 2025 **See also Section 5.1(b).**
Credit Facility: This Warrant to Purchase Stock ("**Warrant**") is issued in connection with that certain First Amendment, of even date herewith, to that certain Loan and Security Agreement dated November 9, 2016, between Silicon Valley Bank and the Company (collectively, and as may be further amended and/or modified and in effect from time to time, the "**Loan Agreement**") and the participation therein of WestRiver Innovation Lending Fund VIII, L.P. pursuant to an arrangement among Silicon Valley Bank, Loan Manager II, LLC and WestRiver Innovation Lending Fund VIII, L.P.

THIS WARRANT CERTIFIES THAT, for good and valuable consideration, [_____] (together with any successor or permitted assignee or transferee of this Warrant or of any shares issued upon exercise hereof, "**Holder**") is entitled to purchase up to such number of fully paid and non-assessable shares of the above-stated Type/Series of Stock (the "**Class**") of the above-named company (the "**Company**") as determined pursuant to Paragraph A below, at the above-stated Warrant Price, all as set forth above and as adjusted pursuant to Section 2 of this Warrant, subject to the provisions and upon the terms and conditions set forth in this Warrant.

A. Number of Shares. This Warrant shall be exercisable for the Initial Shares, plus the Additional Shares, if any (collectively, and as may be adjusted from time to time in accordance with the provisions of this Warrant, the " **Shares**").

(1) Initial Shares. As used herein, " **Initial Shares**" means 7,875 shares of the Class, subject to adjustment from time to time in accordance with the provisions of this Warrant.

(2) Additional Shares. Upon the making of each 2018 Term Loan Advance (as defined in the Loan Agreement) to the Company, this Warrant automatically shall become exercisable for such number of additional shares of the Class as shall equal (a) the Additional Shares Pool, multiplied by (b) a fraction, the numerator of which shall equal the amount of such 2018 Term Loan Advance and the denominator of which shall equal $4,000,000, subject to adjustment thereafter from time to time in accordance with the provisions of this Warrant. All shares, if any, for which this Warrant becomes exercisable pursuant to this Paragraph A(2) are referred to herein cumulatively and collectively, and as may be adjusted from time to time in accordance with the provisions of this Warrant, as the " **Additional Shares**.

(3) Additional Shares Pool. As used herein, " **Additional Shares Pool**" means 23,625 shares of the Class, as such number may be adjusted from time to time in accordance with the provisions of this Warrant (as if the Additional Shares Pool constituted "Shares" hereunder for such purpose at all times from the Issue Date).

SECTION 1. EXERCISE.

1.1 Method of Exercise. Holder may at any time and from time to time exercise this Warrant, in whole or in part, by delivering to the Company the original of this Warrant together with a duly executed Notice of Exercise in substantially the form attached hereto as Appendix 1 and, unless Holder is exercising this Warrant pursuant to a cashless exercise set forth in Section 1.2, a check, wire transfer of same-day funds (to an account designated by the Company), or other form of payment acceptable to the Company for the aggregate Warrant Price for the Shares being purchased.

1.2 Cashless Exercise. On any exercise of this Warrant, in lieu of payment of the aggregate Warrant Price in the manner as specified in Section 1.1 above, but otherwise in accordance with the requirements of Section 1.1, Holder may elect to receive Shares equal to the value of this Warrant, or portion hereof as to which this Warrant is being exercised. Thereupon, the Company shall issue to the Holder such number of fully paid and non-assessable Shares as are computed using the following formula:

$$X = Y(A-B)/A$$

where:

X = the number of Shares to be issued to the Holder;

Y = the number of Shares with respect to which this Warrant is being exercised (inclusive of the Shares surrendered to the Company in payment of the aggregate Warrant Price);

A = the Fair Market Value (as determined pursuant to Section 1.3 below) of one Share; and

B = the Warrant Price.

1.3 Fair Market Value. If shares of the Class are then traded or quoted on a nationally recognized securities exchange, inter-dealer quotation system or over-the-counter market (a "**Trading Market**"), the fair market value of a Share shall be the closing price or last sale price of a share of the Class reported for the Business Day immediately before the date on which Holder delivers this Warrant together with its Notice of Exercise to the Company. If shares of the Class are not then traded in a Trading Market, the Board of Directors of the Company shall determine the fair market value of a Share in its reasonable good faith judgment.

1.4 Delivery of Certificate and New Warrant. Within a reasonable time after Holder exercises this Warrant in the manner set forth in Section 1.1 or 1.2 above, the Company shall deliver, or cause to be delivered, to Holder a certificate, or evidence of a book-entry interest, representing the Shares issued to Holder upon such exercise and, if this Warrant has not been fully exercised and has not expired, a new warrant of like tenor representing the Shares not so acquired.

1.5 Replacement of Warrant. On receipt of evidence reasonably satisfactory to the Company of the loss, theft, destruction or mutilation of this Warrant and, in the case of loss, theft or destruction, on delivery of an indemnity agreement reasonably satisfactory in form, substance and amount to the Company or, in the case of mutilation, on surrender of this Warrant to the Company for cancellation, the Company shall, within a reasonable time, execute and deliver to Holder, in lieu of this Warrant, a new warrant of like tenor and amount.

1.6 Treatment of Warrant Upon Acquisition of Company.

(a) Acquisition. For the purpose of this Warrant, "**Acquisition**" means any transaction or series of related transactions involving: (i) the sale, lease, exclusive license (other than a license permitted under Section 7.1 of the Loan Agreement), or other disposition of all or substantially all of the assets of the Company; (ii) any merger or consolidation of the Company into or with another person or entity (other than a merger or consolidation effected exclusively to change the Company's domicile), or any other corporate reorganization, in which the stockholders of the Company in their capacity as such immediately prior to such merger, consolidation or reorganization, own less than a majority of the Company's (or the surviving or successor entity's) outstanding voting power immediately after such merger, consolidation or reorganization (or, if such Company stockholders beneficially own a majority of the outstanding voting power of the surviving or successor entity as of immediately after such merger, consolidation or reorganization, such surviving or successor entity is not the Company); or (iii) any sale or other transfer by the stockholders of the Company of shares representing at least a majority of the Company's then-total outstanding combined voting power.

(b) Treatment of Warrant at Acquisition. In the event of an Acquisition in which the consideration to be received by the Company's stockholders consists solely of cash, solely of Marketable Securities or a combination of cash and Marketable Securities (a "**Cash/Public Acquisition**"), and the fair market value of one Share as determined in accordance with Section 1.3 above would be greater than the Warrant Price in effect on such date immediately prior to such Cash/Public Acquisition, and Holder has not exercised this Warrant pursuant to Section 1.1 or Section 1.2 above as to all Shares, then this Warrant shall automatically be deemed to be Cashless Exercised pursuant to Section 1.2 above as to all Shares not previously exercised effective immediately prior to and contingent upon the consummation of a Cash/Public Acquisition. In connection with such Cashless Exercise, Holder shall be deemed to have restated each of the representations and warranties in Section 4 of the Warrant as of the date thereof and the Company shall promptly notify the Holder of the number of Shares (or such other securities) issued upon exercise. In the event of a Cash/Public Acquisition where the fair market value of one Share as determined in accordance with Section 1.3 above would be less than the Warrant Price in effect immediately prior to such Cash/Public Acquisition, then this Warrant will expire immediately prior to the consummation of such Cash/Public Acquisition.

(c) Upon the closing of any Acquisition other than a Cash/Public Acquisition, the acquiring, surviving or successor entity shall assume the obligations of this Warrant, and this Warrant shall thereafter be exercisable for the same securities and/or other property as would have been paid for the Shares issuable upon exercise of the unexercised portion of this Warrant as if such Shares were outstanding on and as of the closing of such Acquisition, subject to further adjustment from time to time in accordance with the provisions of this Warrant.

(d) As used in this Warrant, " **Marketable Securities**" means securities meeting all of the following requirements: (i) the issuer thereof is then subject to the reporting requirements of Section

13 or Section 15(d) of the Securities Exchange Act of 1934, as amended (the "**Exchange Act**"), and is then current in its filing of all required reports and other information under the Act and the Exchange Act; (ii) the class and series of shares or other security of the issuer that would be received by Holder in connection with the Acquisition were Holder to exercise this Warrant on or prior to the closing thereof is then traded in a Trading Market, and (iii) following the closing of such Acquisition, Holder would not be restricted from publicly re-selling all of the issuer's shares and/or other securities that would be received by Holder in such Acquisition were Holder to exercise this Warrant in full on or prior to the closing of such Acquisition, except to the extent that any such restriction (x) arises solely under federal or state securities laws, rules or regulations, and (y) does not extend beyond six (6) months from the closing of such Acquisition.

SECTION 2. ADJUSTMENTS TO THE SHARES AND WARRANT PRICE.

2.1 Stock Dividends, Splits, Etc. If the Company declares or pays a dividend or distribution on the outstanding shares of the Class payable in additional shares of the Class or other securities or property (other than cash), then upon exercise of this Warrant, for each Share acquired, Holder shall receive, without additional cost to Holder, the total number and kind of securities and property which Holder would have received had Holder owned the Shares of record as of the date the dividend or distribution occurred. If the Company subdivides the outstanding shares of the Class by reclassification or otherwise into a greater number of shares, the number of Shares purchasable hereunder shall be proportionately increased and the Warrant Price shall be proportionately decreased. If the outstanding shares of the Class are combined or consolidated, by reclassification or otherwise, into a lesser number of shares, the Warrant Price shall be proportionately increased and the number of Shares shall be proportionately decreased.

2.2 Reclassification, Exchange, Combinations or Substitution. Upon any event whereby all of the outstanding shares of the Class are reclassified, exchanged, combined, substituted, or replaced for, into, with or by Company securities of a different class and/or series, then from and after the consummation of such event, this Warrant will be exercisable for the number, class and series of Company securities that Holder would have received had the Shares been outstanding on and as of the consummation of such event, and subject to further adjustment thereafter from time to time in accordance with the provisions of this Warrant. The provisions of this Section 2.2 shall similarly apply to successive reclassifications, exchanges, combinations, substitutions, replacements or other similar events.

2.3 No Fractional Share. No fractional Share shall be issuable upon exercise of this Warrant and the number of Shares to be issued shall be rounded down to the nearest whole Share. If a fractional Share interest arises upon any exercise of the Warrant, the Company shall eliminate such fractional Share interest by paying Holder in cash the amount computed by multiplying the fractional interest by (i) the fair market value (as determined in accordance with Section 1.3 above) of a full Share, less (ii) the then-effective Warrant Price.

2.4 Notice/Certificate as to Adjustments. Upon each adjustment of the Warrant Price, Class and/or number of Shares, the Company, at the Company's expense, shall notify Holder in writing within a reasonable time setting forth the adjustments to the Warrant Price, Class and/or number of Shares and facts upon which such adjustment is based. The Company shall, upon written request from Holder, furnish Holder with a certificate of its Chief Financial Officer or other Company officer having similar duties, including computations of such adjustment and the Warrant Price, Class and number of Shares in effect upon the date of such adjustment.

SECTION 3. REPRESENTATIONS AND COVENANTS OF THE COMPANY.

3.1 Representations and Warranties. The Company represents and warrants to, and agrees with, the Holder as follows:

(a) [Reserved].

(b) All Shares which may be issued upon the exercise of this Warrant shall, upon issuance, be duly authorized, validly issued, fully paid and non-assessable, and free of any liens and encumbrances except for restrictions on transfer provided for herein or under applicable federal and state securities laws. The Company covenants that it shall at all times cause to be reserved and kept available out of its authorized and unissued capital stock such number of shares of the Class and other securities as will be sufficient to permit the exercise in full of this Warrant.

3.2 Notice of Certain Events. If the Company proposes at any time to:

(a) declare any dividend or distribution upon the outstanding shares of the Class, whether in cash, property, stock, or other securities and whether or not a regular cash dividend;

(b) offer for subscription or sale pro rata to the holders of the outstanding shares of the Class any additional shares of any class or series of the Company's stock (other than pursuant to contractual pre-emptive rights);

(c) effect any reclassification, exchange, combination, substitution, reorganization or recapitalization of the outstanding shares of the Class; or

(d) effect an Acquisition or to liquidate, dissolve or wind up;

then, in connection with each such event, the Company shall give Holder notice thereof at the same time and in the same manner as Holder notifies the holders of the outstanding shares of the Class of such event.

SECTION 4. REPRESENTATIONS, WARRANTIES OF THE HOLDER.

The Holder represents and warrants to the Company as follows:

4.1 Purchase for Own Account. This Warrant and the Shares to be acquired upon exercise of this Warrant by Holder are being acquired for investment for Holder's account, not as a nominee or agent, and not with a view to the public resale or distribution within the meaning of the Act. Holder also represents that it has not been formed for the specific purpose of acquiring this Warrant or the Shares.

4.2 Disclosure of Information. Holder is aware of the Company's business affairs and financial condition and has received or has had full access to all the information it considers necessary or appropriate to make an informed investment decision with respect to the acquisition of this Warrant and its underlying securities. Holder further has had an opportunity to ask questions and receive answers from the Company regarding the terms and conditions of the offering of this Warrant and its underlying securities and to obtain additional information (to the extent the Company possessed such information or could acquire it without unreasonable effort or expense) necessary to verify any information furnished to Holder or to which Holder has access.

4.3 Investment Experience. Holder understands that the purchase of this Warrant and its underlying securities involves substantial risk. Holder has experience as an investor in securities of companies in the development stage and acknowledges that Holder can bear the economic risk of such Holder's investment in this Warrant and its underlying securities and has such knowledge and experience in financial or business matters that Holder is capable of evaluating the merits and risks of its investment in this Warrant and its underlying securities and/or has a preexisting personal or business relationship with the Company and certain of its officers, directors or controlling persons of a nature and duration that enables Holder to be aware of the character, business acumen and financial circumstances of such persons.

4.4 Accredited Investor Status. Holder is an "accredited investor" within the meaning of Regulation D promulgated under the Act.

4.5 The Act. Holder understands that this Warrant and the Shares issuable upon exercise hereof have not been registered under the Act in reliance upon a specific exemption therefrom, which exemption depends upon, among other things, the bona fide nature of the Holder's investment intent as expressed herein. Holder understands that this Warrant and the Shares issued upon any exercise hereof must be held indefinitely unless subsequently registered under the Act and qualified under applicable state securities laws, or unless exemption from such registration and qualification are otherwise available. Holder is aware of the provisions of Rule 144 promulgated under the Act.

4.6 No Stockholder Rights. Without limiting any provision of this Warrant, Holder agrees that as a Holder of this Warrant it will not have any rights (including, but not limited to, voting rights) as a stockholder of the Company with respect to the Shares issuable hereunder unless and until the exercise of this Warrant and then only with respect to the Shares issued on such exercise.

SECTION 5. MISCELLANEOUS.

5.1 Term; Automatic Cashless Exercise Upon Expiration.

(a) Term. Subject to the provisions of Section 1.6 above, this Warrant is exercisable in whole or in part at any time and from time to time on or before 6:00 PM, Pacific time, on the Expiration Date and shall be void thereafter.

(b) Automatic Cashless Exercise upon Expiration. In the event that, upon the Expiration Date, the fair market value of one Share as determined in accordance with Section 1.3 above is greater than the Warrant Price in effect on such date, then this Warrant shall automatically be deemed on and as of such date to be exercised pursuant to Section 1.2 above as to all Shares for which it shall not previously have been exercised, and the Company shall, within a reasonable time, deliver a certificate representing the Shares issued upon such exercise to Holder.

5.2 Legends. Each certificate evidencing Shares shall be imprinted with a legend in substantially the following form:

> THE SHARES EVIDENCED BY THIS CERTIFICATE HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "**ACT**"), OR THE SECURITIES LAWS OF ANY STATE AND, EXCEPT AS SET FORTH IN THAT CERTAIN WARRANT TO PURCHASE STOCK ISSUED BY THE ISSUER TO [_____] DATED NOVEMBER

26, 2018, MAY NOT BE OFFERED, SOLD, PLEDGED OR OTHERWISE TRANSFERRED UNLESS AND UNTIL REGISTERED UNDER SAID ACT AND LAWS OR, IN THE OPINION OF LEGAL COUNSEL IN FORM AND SUBSTANCE SATISFACTORY TO THE ISSUER, SUCH OFFER, SALE, PLEDGE OR OTHER TRANSFER IS EXEMPT FROM SUCH REGISTRATION.

5.3 Compliance with Securities Laws on Transfer. This Warrant and the Shares issued upon exercise of this Warrant may not be transferred or assigned in whole or in part except in compliance with applicable federal and state securities laws by the transferor and the transferee (including, without limitation, the delivery of investment representation letters and legal opinions reasonably satisfactory to the Company, as reasonably requested by the Company). The Company shall not require Holder to provide an opinion of counsel if the transfer is to an affiliate of Holder, provided that such affiliate is an "accredited investor" as defined in Regulation D promulgated under the Act.

5.4 Transfer Procedure. Subject to the provisions of Section 5.3 and upon providing the Company with written notice, Holder may transfer all or part of this Warrant or the Shares issued upon exercise of this Warrant to any transferee, provided, however, in connection with any such transfer, Holder will give the Company notice of the portion of the Warrant being transferred with the name, address and taxpayer identification number of the transferee and Holder will surrender this Warrant to the Company for reissuance to the transferee(s) (and Holder if applicable); and provided further, that any transferee shall agree in writing with the Company to be bound by all of the terms and conditions of this Warrant.

5.5 Notices. All notices and other communications hereunder from the Company to the Holder, or vice versa, shall be deemed delivered and effective (i) when given personally, (ii) on the third (3rd) Business Day after being mailed by first-class registered or certified mail, postage prepaid, (iii) upon actual receipt if given by facsimile or electronic mail and such receipt is confirmed in writing by the recipient, or (iv) on the first Business Day following delivery to a reliable overnight courier service, courier fee prepaid, in any case at such address as may have been furnished to the Company or Holder, as the case may be, in writing by the Company or such Holder from time to time in accordance with the provisions of this Section 5.5. All notices to Holder shall be addressed as follows until the Company receives notice of a change of address in connection with a transfer or otherwise:

[_____]
[_____]
Attention: [_____]
Telephone: [_____]
Email: [_____]

With a copy (which shall not constitute notice) to:

[_____]
[_____]
Attention: [_____]
Telephone: [_____]
Email: [_____]

Notice to the Company shall be addressed as follows until Holder receives notice of a change in address:

Axsome Therapeutics, Inc.
Attn: Chief Executive Officer
25 Broadway, 9th Floor
New York, NY 10004
Telephone: (212) 332-3241
Facsimile: (212) 320-0245
Email: htabuteau@axsome.com

With a copy (which shall not constitute notice) to:

DLA Piper LLP (US)
Attn: Jeff Baglio, Esq.
4365 Executive Drive Suite 1100
San Diego, California 92121-2133
Facsimile: (858) 638 5058
Email: jeff.baglio@dlapiper.com

5.6 Waiver. This Warrant and any term hereof may be changed, waived, discharged or terminated (either generally or in a particular instance and either retroactively or prospectively) only by an instrument in writing signed by the party against which enforcement of such change, waiver, discharge or termination is sought.

5.7 Attorneys' Fees. In the event of any dispute between the parties concerning the terms and provisions of this Warrant, the party prevailing in such dispute shall be entitled to collect from the other party all costs incurred in such dispute, including reasonable attorneys' fees.

5.8 Counterparts; Facsimile/Electronic Signatures. This Warrant may be executed in counterparts, all of which together shall constitute one and the same agreement. Any signature page delivered electronically or by facsimile shall be binding to the same extent as an original signature page with regards to any agreement subject to the terms hereof or any amendment thereto.

5.9 Governing Law. This Warrant shall be governed by and construed in accordance with the laws of the State of California, without giving effect to its principles regarding conflicts of law.

5.10 Headings. The headings in this Warrant are for purposes of reference only and shall not limit or otherwise affect the meaning of any provision of this Warrant.

5.11 Business Days. "**Business Day**" is any day that is not a Saturday, Sunday or a day on which banks in Washington are closed.

[Remainder of page left blank intentionally]
[Signature page follows]

IN WITNESS WHEREOF, the parties have caused this Warrant to Purchase Stock to be executed by their duly authorized representatives effective as of the Issue Date written above.

"COMPANY"

AXSOME THERAPEUTICS, INC.

By: _____

Name:_____
(Print)
Title:

"HOLDER"

[_____]

By:_____

APPENDIX 1

NOTICE OF EXERCISE

1.The undersigned Holder hereby exercises its right to purchase _____ shares of the Common/Series _____ Preferred [circle one] Stock of _____ (the " **Company**") in accordance with the attached Warrant To Purchase Stock, and tenders payment of the aggregate Warrant Price for such shares as follows:

[ ] check in the amount of $_____ payable to order of the Company enclosed herewith

[ ] Wire transfer of immediately available funds to the Company's account

[ ] Cashless Exercise pursuant to Section 1.2 of the Warrant

[ ] Other [Describe] _____

2. Please issue a certificate or certificates representing the Shares in the name specified below:

_____
Holder's Name

_____

_____
(Address)

3. By its execution below and for the benefit of the Company, Holder hereby restates each of the representations and warranties in Section 4 of the Warrant to Purchase Stock as of the date hereof.

HOLDER:

_____

By:_____

Name:_____

Title:_____

(Date):_____

THIS WARRANT AND THE SHARES ISSUABLE HEREUNDER HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "**ACT**"), OR THE SECURITIES LAWS OF ANY STATE AND, EXCEPT AS SET FORTH IN SECTIONS 5.3 AND 5.4 BELOW, MAY NOT BE OFFERED, SOLD, PLEDGED OR OTHERWISE TRANSFERRED UNLESS AND UNTIL REGISTERED UNDER SAID ACT AND LAWS OR, IN THE OPINION OF LEGAL COUNSEL IN FORM AND SUBSTANCE SATISFACTORY TO THE ISSUER, SUCH OFFER, SALE, PLEDGE OR OTHER TRANSFER IS EXEMPT FROM SUCH REGISTRATION.

WARRANT TO PURCHASE STOCK

Company: Axsome Therapeutics, Inc., a Delaware corporation
Number of Shares: As set forth in Paragraph A below
Type/Series of Stock: Common Stock, $0.0001 par value per share
Warrant Price: $8.10 per Share, subject to adjustment
Issue Date: March 5, 2019
Expiration Date: March 4, 2026 **See also Section 5.1(b).**
Credit Facility: This Warrant to Purchase Stock ("**Warrant**") is issued in connection with that certain Loan and Security Agreement of even date herewith among Silicon Valley Bank, WestRiver Innovation Lending Fund VIII, L.P. and the Company (as amended and/or modified and in effect from time to time, the "**Loan Agreement**").

THIS WARRANT CERTIFIES THAT, for good and valuable consideration, [_____] (together with any successor or permitted assignee or transferee of this Warrant or of any shares issued upon exercise hereof, "**Holder**") is entitled to purchase up to the number of fully paid and non-assessable shares of the above-stated Type/Series of Stock (the "**Class**") of the above-named company (the "**Company**") determined pursuant to Paragraph A below, at the above-stated Warrant Price, all as set forth above and as adjusted pursuant to Section 2 of this Warrant, subject to the provisions and upon the terms and conditions set forth in this Warrant.

A. Number of Shares. Upon the making (if any) of each Term Loan Advance (as defined in the Loan Agreement) to the Company, this Warrant automatically shall become exercisable for such number of shares of the Class as shall equal (i) the Shares Pool, multiplied by (ii) a fraction, the numerator of which shall equal the amount of such Term Loan Advance and the denominator of which shall equal $24,000,000, subject to adjustment thereafter from time to time in accordance with the provisions of this Warrant. All shares, if any, for which this Warrant becomes exercisable pursuant to this Paragraph A are referred to herein cumulatively and collectively, and as may be adjusted from time to time in accordance with the provisions of this Warrant, as the " **Shares**. As used herein, "**Shares Pool**" means 35,000 shares of the Class, as such number may be adjusted from time to time in accordance with the provisions of this Warrant (as if the Shares Pool constituted "Shares" hereunder at all times from and after the Issue Date hereof for such purpose).

SECTION 1. EXERCISE.

1.1 Method of Exercise. Holder may at any time and from time to time exercise this Warrant, in whole or in part, by delivering to the Company the original of this Warrant together with a duly executed Notice of Exercise in substantially the form attached hereto as Appendix 1 and, unless Holder is exercising this Warrant pursuant to a cashless exercise set forth in Section 1.2, a check, wire

transfer of same-day funds (to an account designated by the Company), or other form of payment acceptable to the Company for the aggregate Warrant Price for the Shares being purchased.

1.2 Cashless Exercise. On any exercise of this Warrant, in lieu of payment of the aggregate Warrant Price in the manner as specified in Section 1.1 above, but otherwise in accordance with the requirements of Section 1.1, Holder may elect to receive Shares equal to the value of this Warrant, or portion hereof as to which this Warrant is being exercised. Thereupon, the Company shall issue to the Holder such number of fully paid and non-assessable Shares as are computed using the following formula:

$$X = Y(A-B)/A$$

where:

X = the number of Shares to be issued to the Holder;

Y = the number of Shares with respect to which this Warrant is being exercised (inclusive of the Shares surrendered to the Company in payment of the aggregate Warrant Price);

A = the Fair Market Value (as determined pursuant to Section 1.3 below) of one Share; and

B = the Warrant Price.

1.3 Fair Market Value. If shares of the Class are then traded or quoted on a nationally recognized securities exchange, inter-dealer quotation system or over-the-counter market (a "**Trading Market**"), the fair market value of a Share shall be the closing price or last sale price of a share of the Class reported for the Business Day immediately before the date on which Holder delivers this Warrant together with its Notice of Exercise to the Company. If shares of the Class are not then traded in a Trading Market, the Board of Directors of the Company shall determine the fair market value of a Share in its reasonable good faith judgment.

1.4 Delivery of Certificate and New Warrant. Within a reasonable time after Holder exercises this Warrant in the manner set forth in Section 1.1 or 1.2 above, the Company shall deliver, or cause to be delivered, to Holder a certificate, or evidence of a book-entry interest, representing the Shares issued to Holder upon such exercise and, if this Warrant has not been fully exercised and has not expired, a new warrant of like tenor representing the Shares not so acquired.

1.5 Replacement of Warrant. On receipt of evidence reasonably satisfactory to the Company of the loss, theft, destruction or mutilation of this Warrant and, in the case of loss, theft or destruction, on delivery of an indemnity agreement reasonably satisfactory in form, substance and amount to the Company or, in the case of mutilation, on surrender of this Warrant to the Company for cancellation, the Company shall, within a reasonable time, execute and deliver to Holder, in lieu of this Warrant, a new warrant of like tenor and amount.

1.6 Treatment of Warrant Upon Acquisition of Company.

(a) Acquisition. For the purpose of this Warrant, "**Acquisition**" means any transaction or series of related transactions involving: (i) the sale, lease, exclusive license (other than a license

permitted under Section 7.1 of the Loan Agreement), or other disposition of all or substantially all of the assets of the Company; (ii) any merger or consolidation of the Company into or with another person or entity (other than a merger or consolidation effected exclusively to change the Company's domicile), or any other corporate reorganization, in which the stockholders of the Company in their capacity as such immediately prior to such merger, consolidation or reorganization, own less than a majority of the Company's (or the surviving or successor entity's) outstanding voting power immediately after such merger, consolidation or reorganization (or, if such Company stockholders beneficially own a majority of the outstanding voting power of the surviving or successor entity as of immediately after such merger, consolidation or reorganization, such surviving or successor entity is not the Company); or (iii) any sale or other transfer by the stockholders of the Company of shares representing at least a majority of the Company's then-total outstanding combined voting power.

(b) Treatment of Warrant at Acquisition. In the event of an Acquisition in which the consideration to be received by the Company's stockholders consists solely of cash, solely of Marketable Securities or a combination of cash and Marketable Securities (a "**Cash/Public Acquisition**"), and the fair market value of one Share as determined in accordance with Section 1.3 above would be greater than the Warrant Price in effect on such date immediately prior to such Cash/Public Acquisition, and Holder has not exercised this Warrant pursuant to Section 1.1 or Section 1.2 above as to all Shares, then this Warrant shall automatically be deemed to be Cashless Exercised pursuant to Section 1.2 above as to all Shares not previously exercised effective immediately prior to and contingent upon the consummation of a Cash/Public Acquisition. In connection with such Cashless Exercise, Holder shall be deemed to have restated each of the representations and warranties in Section 4 of the Warrant as of the date thereof and the Company shall promptly notify the Holder of the number of Shares (or such other securities) issued upon exercise. In the event of a Cash/Public Acquisition where the fair market value of one Share as determined in accordance with Section 1.3 above would be less than the Warrant Price in effect immediately prior to such Cash/Public Acquisition, then this Warrant will expire immediately prior to the consummation of such Cash/Public Acquisition.

(c) Upon the closing of any Acquisition other than a Cash/Public Acquisition, the acquiring, surviving or successor entity shall assume the obligations of this Warrant, and this Warrant shall thereafter be exercisable for the same securities and/or other property as would have been paid for the Shares issuable upon exercise of the unexercised portion of this Warrant as if such Shares were outstanding on and as of the closing of such Acquisition, subject to further adjustment from time to time in accordance with the provisions of this Warrant.

(d) As used in this Warrant, " **Marketable Securities**" means securities meeting all of the following requirements: (i) the issuer thereof is then subject to the reporting requirements of Section 13 or Section 15(d) of the Securities Exchange Act of 1934, as amended (the "**Exchange Act**"), and is then current in its filing of all required reports and other information under the Act and the Exchange Act; (ii) the class and series of shares or other security of the issuer that would be received by Holder in connection with the Acquisition were Holder to exercise this Warrant on or prior to the closing thereof is then traded in a Trading Market, and (iii) following the closing of such Acquisition, Holder would not be restricted from publicly re-selling all of the issuer's shares and/or other securities that would be received by Holder in such Acquisition were Holder to exercise this Warrant in full on or prior to the closing of such Acquisition, except to the extent that any such restriction (x) arises solely under federal or state securities laws, rules or regulations, and (y) does not extend beyond six (6) months from the closing of such Acquisition.

SECTION 2. ADJUSTMENTS TO THE SHARES AND WARRANT PRICE.

2.1 Stock Dividends, Splits, Etc. If the Company declares or pays a dividend or distribution on the outstanding shares of the Class payable in additional shares of the Class or other securities or property (other than cash), then upon exercise of this Warrant, for each Share acquired, Holder shall receive, without additional cost to Holder, the total number and kind of securities and property which Holder would have received had Holder owned the Shares of record as of the date the dividend or distribution occurred. If the Company subdivides the outstanding shares of the Class by reclassification or otherwise into a greater number of shares, the number of Shares purchasable hereunder shall be proportionately increased and the Warrant Price shall be proportionately decreased. If the outstanding shares of the Class are combined or consolidated, by reclassification or otherwise, into a lesser number of shares, the Warrant Price shall be proportionately increased and the number of Shares shall be proportionately decreased.

2.2 Reclassification, Exchange, Combinations or Substitution. Upon any event whereby all of the outstanding shares of the Class are reclassified, exchanged, combined, substituted, or replaced for, into, with or by Company securities of a different class and/or series, then from and after the consummation of such event, this Warrant will be exercisable for the number, class and series of Company securities that Holder would have received had the Shares been outstanding on and as of the consummation of such event, and subject to further adjustment thereafter from time to time in accordance with the provisions of this Warrant. The provisions of this Section 2.2 shall similarly apply to successive reclassifications, exchanges, combinations, substitutions, replacements or other similar events.

2.3 No Fractional Share. No fractional Share shall be issuable upon exercise of this Warrant and the number of Shares to be issued shall be rounded down to the nearest whole Share. If a fractional Share interest arises upon any exercise of the Warrant, the Company shall eliminate such fractional Share interest by paying Holder in cash the amount computed by multiplying the fractional interest by (i) the fair market value (as determined in accordance with Section 1.3 above) of a full Share, less (ii) the then-effective Warrant Price.

2.4 Notice/Certificate as to Adjustments. Upon each adjustment of the Warrant Price, Class and/or number of Shares, the Company, at the Company's expense, shall notify Holder in writing within a reasonable time setting forth the adjustments to the Warrant Price, Class and/or number of Shares and facts upon which such adjustment is based. The Company shall, upon written request from Holder, furnish Holder with a certificate of its Chief Financial Officer or other Company officer having similar duties, including computations of such adjustment and the Warrant Price, Class and number of Shares in effect upon the date of such adjustment.

SECTION 3. REPRESENTATIONS AND COVENANTS OF THE COMPANY.

3.1 Representations and Warranties. The Company represents and warrants to, and agrees with, the Holder as follows:

(a) [Reserved].

(b) All Shares which may be issued upon the exercise of this Warrant shall, upon issuance, be duly authorized, validly issued, fully paid and non-assessable, and free of any liens and encumbrances except for restrictions on transfer provided for herein or under applicable federal and state securities laws. The Company covenants that it shall at all times cause to be reserved and kept available

out of its authorized and unissued capital stock such number of shares of the Class and other securities as will be sufficient to permit the exercise in full of this Warrant.

3.2 Notice of Certain Events. If the Company proposes at any time to:

(a) declare any dividend or distribution upon the outstanding shares of the Class, whether in cash, property, stock, or other securities and whether or not a regular cash dividend;

(b) offer for subscription or sale pro rata to the holders of the outstanding shares of the Class any additional shares of any class or series of the Company's stock (other than pursuant to contractual pre-emptive rights);

(c) effect any reclassification, exchange, combination, substitution, reorganization or recapitalization of the outstanding shares of the Class; or

(d) effect an Acquisition or to liquidate, dissolve or wind up;

then, in connection with each such event, the Company shall give Holder notice thereof at the same time and in the same manner as Holder notifies the holders of the outstanding shares of the Class of such event.

SECTION 4. REPRESENTATIONS, WARRANTIES OF THE HOLDER.

The Holder represents and warrants to the Company as follows:

4.1 Purchase for Own Account. This Warrant and the Shares to be acquired upon exercise of this Warrant by Holder are being acquired for investment for Holder's account, not as a nominee or agent, and not with a view to the public resale or distribution within the meaning of the Act. Holder also represents that it has not been formed for the specific purpose of acquiring this Warrant or the Shares.

4.2 Disclosure of Information. Holder is aware of the Company's business affairs and financial condition and has received or has had full access to all the information it considers necessary or appropriate to make an informed investment decision with respect to the acquisition of this Warrant and its underlying securities. Holder further has had an opportunity to ask questions and receive answers from the Company regarding the terms and conditions of the offering of this Warrant and its underlying securities and to obtain additional information (to the extent the Company possessed such information or could acquire it without unreasonable effort or expense) necessary to verify any information furnished to Holder or to which Holder has access.

4.3 Investment Experience. Holder understands that the purchase of this Warrant and its underlying securities involves substantial risk. Holder has experience as an investor in securities of companies in the development stage and acknowledges that Holder can bear the economic risk of such Holder's investment in this Warrant and its underlying securities and has such knowledge and experience in financial or business matters that Holder is capable of evaluating the merits and risks of its investment in this Warrant and its underlying securities and/or has a preexisting personal or business relationship with the Company and certain of its officers, directors or controlling persons of a nature and duration that enables Holder to be aware of the character, business acumen and financial circumstances of such persons.

4.4 Accredited Investor Status. Holder is an "accredited investor" within the meaning of Regulation D promulgated under the Act.

4.5 The Act. Holder understands that this Warrant and the Shares issuable upon exercise hereof have not been registered under the Act in reliance upon a specific exemption therefrom, which exemption depends upon, among other things, the bona fide nature of the Holder's investment intent as expressed herein. Holder understands that this Warrant and the Shares issued upon any exercise hereof must be held indefinitely unless subsequently registered under the Act and qualified under applicable state securities laws, or unless exemption from such registration and qualification are otherwise available. Holder is aware of the provisions of Rule 144 promulgated under the Act.

4.6 No Stockholder Rights. Without limiting any provision of this Warrant, Holder agrees that as a Holder of this Warrant it will not have any rights (including, but not limited to, voting rights) as a stockholder of the Company with respect to the Shares issuable hereunder unless and until the exercise of this Warrant and then only with respect to the Shares issued on such exercise.

SECTION 5. MISCELLANEOUS.

5.1 Term; Automatic Cashless Exercise Upon Expiration.

(a) Term. Subject to the provisions of Section 1.6 above, this Warrant is exercisable in whole or in part at any time and from time to time on or before 6:00 PM, Pacific time, on the Expiration Date and shall be void thereafter.

(b) Automatic Cashless Exercise upon Expiration. In the event that, upon the Expiration Date, the fair market value of one Share as determined in accordance with Section 1.3 above is greater than the Warrant Price in effect on such date, then this Warrant shall automatically be deemed on and as of such date to be exercised pursuant to Section 1.2 above as to all Shares for which it shall not previously have been exercised, and the Company shall, within a reasonable time, deliver a certificate representing the Shares issued upon such exercise to Holder.

5.2 Legends. Each certificate evidencing Shares shall be imprinted with a legend in substantially the following form:

> THE SHARES EVIDENCED BY THIS CERTIFICATE HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "**ACT**"), OR THE SECURITIES LAWS OF ANY STATE AND, EXCEPT AS SET FORTH IN THAT CERTAIN WARRANT TO PURCHASE STOCK ISSUED BY THE ISSUER TO [_____] DATED MARCH 5, 2019 MAY NOT BE OFFERED, SOLD, PLEDGED OR OTHERWISE TRANSFERRED UNLESS AND UNTIL REGISTERED UNDER SAID ACT AND LAWS OR, IN THE OPINION OF LEGAL COUNSEL IN FORM AND SUBSTANCE SATISFACTORY TO THE ISSUER, SUCH OFFER, SALE, PLEDGE OR OTHER TRANSFER IS EXEMPT FROM SUCH REGISTRATION.

5.3 Compliance with Securities Laws on Transfer. This Warrant and the Shares issued upon exercise of this Warrant may not be transferred or assigned in whole or in part except in compliance with applicable federal and state securities laws by the transferor and the transferee (including, without limitation, the delivery of investment representation letters and legal opinions reasonably satisfactory to the Company, as reasonably requested by the Company). The Company shall not require Holder to

provide an opinion of counsel if the transfer is to an affiliate of Holder, provided that such affiliate is an "accredited investor" as defined in Regulation D promulgated under the Act.

5.4 Transfer Procedure. Subject to the provisions of Section 5.3 and upon providing the Company with written notice, Holder may transfer all or part of this Warrant or the Shares issued upon exercise of this Warrant to any transferee, provided, however, in connection with any such transfer, Holder will give the Company notice of the portion of the Warrant being transferred with the name, address and taxpayer identification number of the transferee and Holder will surrender this Warrant to the Company for reissuance to the transferee(s) (and Holder if applicable); and provided further, that any transferee shall agree in writing with the Company to be bound by all of the terms and conditions of this Warrant.

5.5 Notices. All notices and other communications hereunder from the Company to the Holder, or vice versa, shall be deemed delivered and effective (i) when given personally, (ii) on the third (3rd) Business Day after being mailed by first-class registered or certified mail, postage prepaid, (iii) upon actual receipt if given by facsimile or electronic mail and such receipt is confirmed in writing by the recipient, or (iv) on the first Business Day following delivery to a reliable overnight courier service, courier fee prepaid, in any case at such address as may have been furnished to the Company or Holder, as the case may be, in writing by the Company or such Holder from time to time in accordance with the provisions of this Section 5.5. All notices to Holder shall be addressed as follows until the Company receives notice of a change of address in connection with a transfer or otherwise:

[_____]
[_____]
Attention: [_____]
Telephone: [_____]
Email: [_____]

With a copy (which shall not constitute notice) to:

[_____]
[_____]
Attention: [_____]
Telephone: [_____]
Email: [_____]

Notice to the Company shall be addressed as follows until Holder receives notice of a change in address:

Axsome Therapeutics, Inc.
Attn: Chief Executive Officer
25 Broadway, 9th Floor
New York, NY 10004
Telephone: (212) 332-3241
Facsimile: (212) 320-0245
Email: htabuteau@axsome.com

With a copy (which shall not constitute notice) to:

DLA Piper LLP (US)
Attn: Emilio Ragosa, Esq.
51 John F. Kennedy Parkway, Suite 120
Short Hills, New Jersey 07078-2704
Facsimile: (973) 215-2804
Email: emilio.ragosa@dlapiper.com

5.6 Waiver. This Warrant and any term hereof may be changed, waived, discharged or terminated (either generally or in a particular instance and either retroactively or prospectively) only by an instrument in writing signed by the party against which enforcement of such change, waiver, discharge or termination is sought.

5.7 Attorneys' Fees. In the event of any dispute between the parties concerning the terms and provisions of this Warrant, the party prevailing in such dispute shall be entitled to collect from the other party all costs incurred in such dispute, including reasonable attorneys' fees.

5.8 Counterparts; Facsimile/Electronic Signatures. This Warrant may be executed in counterparts, all of which together shall constitute one and the same agreement. Any signature page delivered electronically or by facsimile shall be binding to the same extent as an original signature page with regards to any agreement subject to the terms hereof or any amendment thereto.

5.9 Governing Law. This Warrant shall be governed by and construed in accordance with the laws of the State of California, without giving effect to its principles regarding conflicts of law.

5.10 Headings. The headings in this Warrant are for purposes of reference only and shall not limit or otherwise affect the meaning of any provision of this Warrant.

5.11 Business Days. "**Business Day**" is any day that is not a Saturday, Sunday or a day on which banks in Washington are closed.

[Remainder of page left blank intentionally]
[Signature page follows]

IN WITNESS WHEREOF, the parties have caused this Warrant to Purchase Stock to be executed by their duly authorized representatives effective as of the Issue Date written above.

"COMPANY"

AXSOME THERAPEUTICS, INC.

By: _____

Name:_____
(Print)
Title:

"HOLDER"

[_____]

By:_____

APPENDIX 1

NOTICE OF EXERCISE

1.The undersigned Holder hereby exercises its right to purchase _____ shares of the Common/Series _____ Preferred [circle one] Stock of _____ (the " **Company**") in accordance with the attached Warrant To Purchase Stock, and tenders payment of the aggregate Warrant Price for such shares as follows:

[ ] check in the amount of $_____ payable to order of the Company enclosed herewith

[ ] Wire transfer of immediately available funds to the Company's account

[ ] Cashless Exercise pursuant to Section 1.2 of the Warrant

[ ] Other [Describe] _____

2. Please issue a certificate or certificates representing the Shares in the name specified below:

_____
Holder's Name

_____

_____
(Address)

3. By its execution below and for the benefit of the Company, Holder hereby restates each of the representations and warranties in Section 4 of the Warrant to Purchase Stock as of the date hereof.

HOLDER:

_____

By:_____

Name:_____

Title:_____

(Date):_____

FIRST AMENDMENT
TO
LOAN AND SECURITY AGREEMENT

This First Amendment to Loan and Security Agreement (this "**Amendment**") is entered into this 26th day of November, 2018, by and between **SILICON VALLEY BANK** ("**Bank**") and **AXSOME THERAPEUTICS, INC.**, a Delaware corporation ("**Borrower**") whose address is 25 Broadway, 9th Floor, New York, New York 10004.

Recitals

A. Bank and Borrower have entered into that certain Loan and Security Agreement dated as of November 9, 2016 (as the same may from time to time be amended, modified, supplemented or restated, the "**Loan Agreement**").

B. Bank has extended credit to Borrower for the purposes permitted in the Loan Agreement.

C. Borrower has requested that Bank amend the Loan Agreement to (i) extend a new term loan to Borrower, (ii) consent to the Subsidiary Formation (as defined herein), (iii) waive the Stated Default (as defined herein), and (iv) make certain other revisions to the Loan Agreement as more fully set forth herein.

D. Bank has agreed to so amend certain provisions of the Loan Agreement, but only to the extent, in accordance with the terms, subject to the conditions and in reliance upon the representations and warranties set forth below.

Agreement

Now, Therefore, in consideration of the foregoing recitals and other good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, and intending to be legally bound, the parties hereto agree as follows:

1. Definitions. Capitalized terms used but not defined in this Amendment shall have the meanings given to them in the Loan Agreement.

2. Amendments to Loan Agreement.

2.1 Section 2.1.2 (2018 Term Loan Advance). The Loan Agreement shall be amended by inserting the following new section to appear immediately following Section 2.1.1:

2.1.2 2018 Term Loan Advance.

(a) Availability. Subject to the terms and conditions of this Agreement, during the 2018 Draw Period, Bank shall make one (1) advance (the "**2018 Term Loan Advance**") available to Borrower in an original principal amount equal to Four Million Dollars ($4,000,000.00). After repayment, the 2018 Term Loan Advance (or any portion thereof) may not be reborrowed.

(b) Interest Period. Commencing on the first (1st) Payment Date of the month following the month in which the Funding Date of the 2018 Term Loan Advance occurs, and continuing on each Payment Date thereafter, Borrower shall make monthly payments of interest on the principal amount of the 2018 Term Loan Advance at the rate set forth in Section 2.2(a).

(c) Repayment. Commencing on the 2018 Term Loan Amortization Date, and continuing on each Payment Date thereafter, Borrower shall repay the 2018 Term Loan Advance in (i) equal consecutive monthly installments of principal based on the 2018 Repayment Schedule, plus (ii) monthly payments of accrued interest at the rate set forth in Section 2.2(a). All outstanding principal and accrued and unpaid interest with respect to the 2018 Term Loan Advance, and all other outstanding Obligations with respect to the 2018 Term Loan Advance, are due and payable in full on the Term Loan Maturity Date.

(d) Permitted Prepayment of the 2018 Term Loan Advance. Borrower shall have the option to prepay all, but not less than all, of the 2018 Term Loan Advance advanced by Bank under this Agreement, provided Borrower (i) provides written notice to Bank of its election to prepay the 2018 Term Loan Advance at least ten (10) days prior to such prepayment, and (ii) pays, on the date of such prepayment (A) all outstanding principal plus accrued and unpaid interest, (B) the 2018 Final Payment, (C) the 2018 Prepayment Premium, plus (D) all other sums, if any, that shall have become due and payable, including interest at the Default Rate with respect to any past due amounts.

(e) Mandatory Prepayment Upon an Acceleration. If the 2018 Term Loan Advance is accelerated following the occurrence of an Event of Default, Borrower shall immediately pay to Bank an amount equal to the sum of: (i) all outstanding principal plus accrued and unpaid interest, (ii) the 2018 Final Payment, (iii) the 2018 Prepayment Premium, plus (iv) all other sums, if any, that shall have become due and payable, including interest at the Default Rate with respect to any past due amounts."

2.2 Section 2.2(a) (Interest Rate). Section 2.2(a) of the Loan Agreement is deleted in its entirety and replaced with the following:

(a) Interest Rate. Subject to Section 2.2(b), the principal amount outstanding for (i) each Term Loan Advance shall accrue interest at a floating per annum rate equal to four and one-half of one percent (4.50%) above the Prime Rate and (ii) the 2018 Term Loan Advance shall accrue interest at a floating per annum rate equal to the greater of (A) two percent (2.00%) above the Prime Rate and (B) seven and one-quarter of one percent (7.25%), which interest, in each case, shall be payable monthly in accordance with Section 2.2(d) below."

2.3 Section 2.3 (Fees). Section 2.3 is amended by inserting the following new subsections immediately following subsection (e) to appear as subsections (f) and (g) thereof:

(e) 2018 Final Payment. The 2018 Final Payment, when due hereunder.

(f) 2018 Prepayment Premium. The 2018 Prepayment Premium, when due hereunder."

2.4 Section 6.2 (**Financial Statements, Reports, Certificates**). Section 6.2 is amended by (i) deleting the text "and" appearing at the end of subsection (h) thereof, (ii) re-lettering subsection (i) to appear as subsection (j) thereof, and (iii) inserting the following new subsection to appear as new subsection (i) thereof:

(i) Beneficial Ownership Information. Prompt written notice of any changes to the beneficial ownership information set out in Section 14 of the Perfection Certificate. Borrower understands and acknowledges that Bank relies on such true, accurate and up-to-date beneficial ownership information to meet Bank's regulatory obligations to obtain, verify and record information about the beneficial owners of its legal entity customers; and"

2.5 Section 6.6(a) (Operating Accounts). Subsections (a) and (b) of Section 6.6 of the Loan Agreement are deleted in their entirety and replaced with the following:

(a) Maintain all of its and all of its Subsidiaries' operating, depository and securities accounts with Bank and Bank's Affiliates; provided that, Borrower may maintain one (1) account with CitiBank, so long as such account does not contain more than Ten Thousand Dollars ($10,000.00) in the aggregate any time (the "**CitiBank Account**"). Notwithstanding the foregoing, Australian Subsidiary and Irish Subsidiary may maintain accounts outside of the United States with financial institutions other than Bank and Bank's Affiliates, provided that the maximum aggregate balance in all such accounts shall not exceed One Hundred Fifty Thousand Dollars ($150,000.00) at any time.

(b) Provide Bank five (5) days prior written notice before establishing any Collateral Account at or with any bank or financial institution other than Bank or Bank's Affiliates. For each Collateral Account that Borrower at any time maintains, Borrower shall cause the applicable bank or financial institution (other than Bank) at or with which any Collateral Account is maintained to execute and deliver a Control Agreement or other appropriate instrument with respect to such Collateral Account to perfect Bank's Lien in such Collateral Account in accordance with the terms hereunder which Control Agreement may not be terminated without the prior written consent of Bank. The provisions of the previous sentence shall not apply (i) to the CitiBank Account or (ii) to deposit accounts exclusively used for payroll, payroll taxes and other employee wage and benefit payments to or for the benefit of Borrower's employees and identified to Bank by Borrower as such."

2.6 Section 13.1 (**Definitions**). The Loan Agreement is amended by deleting subsection (h) of the definition of "Permitted Investments" in its entirety and replacing it with the

following:

(h) Investments (i) by Borrower in Australian Subsidiary for ordinary, necessary and current operating expenses not to exceed One Million Five Hundred Thousand Dollars ($1,500,000.00) in the aggregate in any fiscal year and (ii) by Borrower in Irish Subsidiary for ordinary, necessary and current operating expenses not to exceed Fifty Thousand Dollars ($50,000.00) in the aggregate in any fiscal year, provided, in each case, no Event of Default has occurred and is continuing at the time of such Investments or would result from such Investments; and"

2.7 Section 13.1 (**Definitions**). The Loan Agreement is amended by deleting the following term and its respective definition set forth in Section 13.1 in its entirety and replacing it with the following:

"**Credit Extension**" is any Term Loan Advance, the 2018 Term Loan Advance, or any other extension of credit by Bank for Borrower's benefit."

"**Obligations**" are Borrower's obligations to pay when due any debts, principal, interest, fees, the Final Payment, the Prepayment Premium, the 2018 Final Payment, the 2018 Prepayment Premium, Bank Expenses, and other amounts Borrower owes Bank now or later, whether under this Agreement, the other Loan Documents (other than the Warrant), or otherwise, including, without limitation, any interest accruing after Insolvency Proceedings begin and debts, liabilities, or obligations of Borrower assigned to Bank, and to perform Borrower's duties under the Loan Documents (other than the Warrant)."

"**Warrant**" is, collectively, (i) that certain Warrant to Purchase Stock dated as of November 9, 2016, between Borrower and Bank, (ii) that certain Warrant to Purchase Stock dated as of November 9, 2016, between Borrower and Life Science Loans, LLC, (iii) that certain Warrant to Purchase Stock dated as of the First Amendment Effective Date, between Borrower and Bank, and (iv) that certain Warrant to Purchase Stock dated as of the First Amendment Effective Date, between Borrower and WestRiver Innovation Lending Fund VIII, L.P., in each case, as may be amended, modified, supplemented, or restated from time to time."

2.8 Section 13 (**Definitions**). The Loan Agreement is amended by inserting the following new terms and their respective definitions to appear alphabetically in Section 13.1 thereof:

"**2018 Draw Period**" is the period of time commencing upon the occurrence of the 2018 Milestone Event and continuing through May 31, 2019."

"**2018 Final Payment**" is a payment (in addition to and not in substitution for the regular monthly payments of principal plus accrued interest) equal to the original principal amount of the 2018 Term Loan Advance extended by Bank to

Borrower hereunder multiplied by seven percent (7.00%), due on the earliest to occur of (a) the Term Loan Maturity Date, (b) as required pursuant to Section 2.1.2(d) or 2.1.2(e), (c) the payment in full of the 2018 Term Loan Advance or (d) the termination of this Agreement.

"**2018 Milestone Event**" means Borrower has provided Bank with evidence, after the First Amendment Effective Date, but on or prior to May 31, 2019, satisfactory to Bank in its sole and absolute discretion that Borrower: (i) has received positive data with respect to Borrower's phase 2 clinical trial of AXS-12, sufficient to submit a phase 3 protocol to the FDA, and (ii) has not received any objections from the FDA within thirty (30) days after submission of such phase 3 protocol."

"**2018 Prepayment Premium**" shall be an additional fee payable to Bank in amount equal to:

(a) for a prepayment of the 2018 Term Loan Advance made on or prior to the first (1st) anniversary of the First Amendment Effective Date, two and one-half of one percent (2.50%) of the then outstanding principal amount of the 2018 Term Loan Advance as of the date immediately and prior to such prepayment; and

(b) for a prepayment of the 2018 Term Loan Advance made after the first (1st) anniversary of the First Amendment Effective Date, but prior to the Term Loan Maturity Date, one and one-half of one percent (1.50%) of the then outstanding principal amount of the 2018 Term Loan Advance as of the date immediately and prior to such prepayment."

"**2018 Repayment Schedule**" means the period of time equal to eighteen (18) consecutive months; provided, however, that upon the occurrence of the Interest Only Extension Event, the 2018 Repayment Schedule shall mean the period of time equal to twelve (12) consecutive months."

"**2018 Term Loan Advance**" is defined in Section 2.1.2(a)."

"**2018 Term Loan Amortization Date**" is June 1, 2019; provided that, upon the occurrence of the Interest Only Extension Event, the 2018 Term Loan Amortization Date is December 1, 2019."

"**AXS-12**" means Borrower's AXS-12 product candidate for the treatment of narcolepsy."

"**CitiBank Account**" is defined in Section 6.6(a)."

"**First Amendment Effective Date**" is November 26, 2018.

"**Interest Only Extension Event**" means Borrower has provided Bank with evidence, on or prior to May 31, 2019, satisfactory to Bank in its reasonable discretion that, Borrower has received, after the First Amendment Effective Date, but on or prior to May 31, 2019, unrestricted and unencumbered (other than Liens in favor of Bank pursuant to the general security interest granted under this Agreement) net cash proceeds in an aggregate amount of at least Twenty Million Dollars ($20,000,000.00) from (a) Subordinated Debt or other similar agreements in form and substance acceptable to Bank and/or (b) partnerships, collaborations, and/or licensing agreements, each of which shall be of the types permitted under the terms of this Agreement and in form and substance acceptable to Bank."

"**Irish Subsidiary**" is a wholly owned Subsidiary of Borrower to be formed in the future under the laws of Ireland."

2.9 Exhibit A (**Collateral Description**). The Collateral description appearing as Exhibit A to the Loan Agreement is deleted in its entirety and replaced with the Collateral description attached as Schedule 1 hereto.

3. Limitation of Amendments.

3.1 The amendments set forth in Section 2 above are effective for the purposes set forth herein and shall be limited precisely as written and shall not be deemed to (a) be a consent to any amendment, waiver or modification of any other term or condition of any Loan Document, or (b) otherwise prejudice any right or remedy which Bank may now have or may have in the future under or in connection with any Loan Document.

3.2 This Amendment shall be construed in connection with and as part of the Loan Documents and all terms, conditions, representations, warranties, covenants and agreements set forth in the Loan Documents, except as herein amended, are hereby ratified and confirmed and shall remain in full force and effect.

4. Consent. Borrower has notified Bank that Borrower has created or will create an Irish Subsidiary (the "**Subsidiary Formation**"). Borrower has requested that Bank consent to the Subsidiary Formation. Bank hereby consents to the Subsidiary Formation and agrees that the Subsidiary Formation shall not, in and of itself, constitute an "Event of Default" under Section 7.3 (relative to mergers or acquisitions), Section 7.7 (relative to distributions and Investments), or Section 7.8 (relative to transactions with Affiliates) of the Loan Agreement. Borrower hereby acknowledges and agrees that nothing in this Section or anywhere in this Amendment shall be deemed or otherwise construed as a waiver by Bank of any of its rights and remedies pursuant to the Loan Documents, applicable law or otherwise.

5. Waiver. Bank hereby waives Borrower's existing default under Section 6.6(a) of the Loan Agreement (as in effect prior to giving effect to this Amendment) by virtue of Borrower's failure to maintain at all times, after the expiration of the Transition Period, all of its and its Subsidiaries' operating, depository and securities accounts with Bank and Bank's Affiliates (the "**Stated Default**"). Borrower hereby acknowledges and agrees that except as specifically provided herein, nothing in this Section or anywhere in this Waiver shall be deemed or otherwise construed

as a waiver by Bank of any of its rights and remedies pursuant to the Loan Documents, applicable law or otherwise. The foregoing waiver shall apply only to the Stated Default and shall not be construed as a waiver or agreement to waive any other defaults or Events of Default.

6. Representations and Warranties. To induce Bank to enter into this Amendment, Borrower hereby represents and warrants to Bank as follows:

6.1 Immediately after giving effect to this Amendment (a) the representations and warranties contained in the Loan Documents are true, accurate and complete in all material respects as of the date hereof (except to the extent such representations and warranties relate to an earlier date, in which case they are true and correct as of such date), and (b) no Event of Default has occurred and is continuing;

6.2 Borrower has the power and authority to execute and deliver this Amendment and to perform its obligations under the Loan Agreement, as amended by this Amendment;

6.3 The organizational documents of Borrower delivered to Bank on the Effective Date remain true, accurate and complete and have not been amended, supplemented or restated and are and continue to be in full force and effect;

6.4 The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, have been duly authorized;

6.5 The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not and will not contravene (a) any law or regulation binding on or affecting Borrower, (b) any contractual restriction with a Person binding on Borrower, (c) any order, judgment or decree of any court or other governmental or public body or authority, or subdivision thereof, binding on Borrower, or (d) the organizational documents of Borrower;

6.6 The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not require any order, consent, approval, license, authorization or validation of, or filing, recording or registration with, or exemption by any governmental or public body or authority, or subdivision thereof, binding on Borrower, except as already has been obtained or made; and

6.7 This Amendment has been duly executed and delivered by Borrower and is the binding obligation of Borrower, enforceable against Borrower in accordance with its terms, except as such enforceability may be limited by bankruptcy, insolvency, reorganization, liquidation, moratorium or other similar laws of general application and equitable principles relating to or affecting creditors' rights.

7. Perfection Certificate. Borrower hereby ratifies, confirms and reaffirms, all and singular, the terms and disclosures contained in a certain Perfection Certificate dated as of November 9, 2016, as amended by Schedule 2 hereto (the "**Perfection Certificate**"), and

acknowledges, confirms and agrees the disclosures and information Borrower provided to Bank in the Perfection Certificate have not changed, as of the date hereof. Borrower hereby agrees that all references in the Loan Agreement to the "Perfection Certificate" shall hereinafter be deemed to be references to the Perfection Certificate as defined herein.

8. Post-Closing Condition. Within thirty (30) days of the date of this Amendment, Borrower shall deliver to Bank, in form and substance acceptable to Bank, a notice of cancellation insurance endorsement as required by Section 6.5 of the Loan Agreement.

9. Integration. This Amendment and the Loan Documents represent the entire agreement about this subject matter and supersede prior negotiations or agreements. All prior agreements, understandings, representations, warranties, and negotiations between the parties about the subject matter of this Amendment and the Loan Documents merge into this Amendment and the Loan Documents.

10. No Defenses of Borrower. To induce Bank to enter into this Amendment, Borrower hereby represents and warrants to Bank that Borrower has no known offsets, defenses, claims or counterclaims against Bank with respect to the Obligations.

11. Counterparts. This Amendment may be executed in any number of counterparts and all of such counterparts taken together shall be deemed to constitute one and the same instrument.

12. Effectiveness. This Amendment shall be deemed effective upon (a) the due execution and delivery to Bank of this Amendment by each party hereto, and (b) Borrower's payment to Bank of Bank's reasonable and documented legal fees and expenses incurred in connection with this Amendment.

[Signature page follows.]

In Witness Whereof, the undersigned have executed this Amendment as a sealed instrument under the laws of the Commonwealth of Massachusetts as of the date first above written.

BANK	**BORROWER**
SILICON VALLEY BANK	AXSOME THERAPEUTICS, INC.
By: /s/ Ryan Roller	By: /s/ Herriot Tabuteau, M.D.
Name: Ryan Roller	Name: Herriot Tabuteau, M.D.
Title: Vice President	Title: Chief Executive Officer

The undersigned hereby certifies, to the best of his or her knowledge, that the information set out in the Perfection Certificate is true, complete and correct.

AXSOME THERAPEUTICS, INC.

By: /s/ Herriot Tabuteau, M.D.

Name: Herriot Tabuteau, M.D.
Title: Chief Executive Officer

Schedule 1

EXHIBIT A – COLLATERAL DESCRIPTION

The Collateral consists of all of Borrower's right, title and interest in and to the following personal property:

All goods, Accounts (including health-care receivables), Equipment, Inventory, contract rights or rights to payment of money, leases, license agreements, franchise agreements, General Intangibles (except as provided below), commercial tort claims, documents, instruments (including any promissory notes), chattel paper (whether tangible or electronic), cash, deposit accounts, certificates of deposit, fixtures, letters of credit rights (whether or not the letter of credit is evidenced by a writing), securities, and all other investment property, supporting obligations, and financial assets, whether now owned or hereafter acquired, wherever located; and

all Borrower's Books relating to the foregoing, and any and all claims, rights and interests in any of the above and all substitutions for, additions, attachments, accessories, accessions and improvements to and replacements, products, proceeds and insurance proceeds of any or all of the foregoing.

Notwithstanding the foregoing, the Collateral does not include (i) more than sixty-five percent (65.0%) of the presently existing and hereafter arising issued and outstanding shares of capital stock owned by Borrower of Australian Subsidiary and Irish Subsidiary which shares entitle the holder thereof to vote for directors or any other matter, (ii) rights held under a license that are not assignable by their terms without the consent of the licensor thereof (but only to the extent such restriction on assignment is enforceable under applicable law), or (iii) any Intellectual Property; provided, however, the Collateral shall include all Accounts and all proceeds of Intellectual Property. If a judicial authority (including a U.S. Bankruptcy Court) would hold that a security interest in the underlying Intellectual Property is necessary to have a security interest in such Accounts and such property that are proceeds of Intellectual Property, then the Collateral shall automatically, and effective as of the Effective Date, include the Intellectual Property to the extent necessary to permit perfection of Bank's security interest in such Accounts and such other property of Borrower that are proceeds of the Intellectual Property.

Pursuant to the terms of a certain negative pledge arrangement with Bank, Borrower has agreed not to encumber any of its Intellectual Property in violation of this Agreement without Bank's prior written consent.

LOAN AND SECURITY AGREEMENT

THIS LOAN AND SECURITY AGREEMENT (this "Agreement") dated as of March 5, 2019 (the "**Effective Date**"), among (a) **SILICON VALLEY BANK**, a California corporation ("**SVB**"), in its capacity as administrative agent and collateral agent ("**Agent**"), (b) **SILICON VALLEY BANK**, a California corporation, as a lender, (c) **WESTRIVER INNOVATION LENDING FUND VIII, L.P.**, a Delaware limited partnership ("**WestRiver**"), as a lender (SVB and WestRiver and each of the other "Lenders" from time to time a party hereto are referred to herein collectively as the "**Lenders**" and each individually as a "**Lender**"), and (d) **AXSOME THERAPEUTICS, INC.**, a Delaware corporation ("**Borrower**"), provides the terms on which Agent and the Lenders shall lend to Borrower, and Borrower shall repay Agent and the Lenders. The parties agree as follows:

1 ACCOUNTING AND OTHER TERMS

Accounting terms not defined in this Agreement shall be construed following GAAP. Calculations and determinations must be made following GAAP. Capitalized terms not otherwise defined in this Agreement shall have the meanings set forth in Section 14 of this Agreement. All other terms contained in this Agreement, unless otherwise indicated, shall have the meaning provided by the Code to the extent such terms are defined therein.

2 LOAN AND TERMS OF PAYMENT

2.1 Promise to Pay. Borrower hereby unconditionally promises to pay to Agent, for the ratable benefit of each Lender, the outstanding principal amount of all Credit Extensions advanced to Borrower by such Lender and accrued and unpaid interest thereon, together with any fees as and when due in accordance with this Agreement.

2.2 Term Loan Advances.

(a) Availability. Subject to the terms and conditions of this Agreement, upon Borrower's request, the Lenders, severally and not jointly, shall make one (1) term loan advance to Borrower on or about the Effective Date in an original principal amount of Twenty Million Dollars ($20,000,000.00) according to each Lender's Term Loan Commitment as set forth on Schedule 1.1 hereto (the "**Term A Loan Advance**"), provided that all or a portion of the Term A Loan Advance shall be used to repay in full all of Borrower's outstanding obligations and liabilities in respect of the Term Loan Advances to SVB under the Existing Loan Agreement (including, without limitation, the "Final Payment" as defined in the Existing Loan Agreement) (the "**SVB Obligations**"). Borrower hereby authorizes Agent to apply such proceeds to the SVB Obligations as part of the funding process without actually depositing such funds into an account of Borrower. Borrower hereby acknowledges, confirms and agrees that (i) as of the Effective Date, there is no availability remaining under the Existing Loan Agreement and (ii) upon payment in full of the SVB Obligations, the Existing Loan Agreement will be terminated. Subject to the terms and conditions of this Agreement, upon Borrower's request, during the Draw Period, the Lenders, severally and not jointly, shall make one (1) term loan advance available to Borrower in an original principal amount of Four Million Dollars ($4,000,000.00) according to each Lender's Term Loan Commitment as set forth on Schedule 1.1 hereto (the "**Term B Loan Advance**"). The Term A Loan Advance and the Term B Loan Advance are hereinafter referred to singly as the "**Term Loan Advance**" and collectively as the "**Term Loan Advances**". After repayment, no Term Loan Advance (or any portion thereof) may be reborrowed.

(b) Interest Payments. With respect to each Term Loan Advance, commencing on the first (1st) Payment Date following the Funding Date of such Term Loan Advance and continuing on the Payment Date of each month thereafter, Borrower shall make monthly payments of interest to Agent, for the account of the Lenders, in arrears, on the principal amount of each Term Loan Advance, at the rate set forth in Section 2.3(a).

(c) Repayment of the Term Loan Advances. Commencing on the Term Loan Amortization Date, and continuing on each Payment Date thereafter, Borrower shall repay the aggregate outstanding Term Loan Advances to Agent, for the account of the Lenders, in (i) consecutive equal monthly installments of principal based on the Repayment Schedule, plus (ii) monthly payments of accrued interest at the rate set forth in Section 2.3(a). All outstanding principal and accrued and unpaid interest with respect to the Term Loan Advances, and all other outstanding Obligations under the Term Loan Advances, are due and payable in full on the Term Loan Maturity Date.

(d) Permitted Prepayment. Borrower shall have the option to prepay all, but not less than all, of the Term Loan Advances advanced by the Lenders under this Agreement, provided Borrower (i) delivers written notice to Agent of its election to prepay the Term Loan Advances at least thirty (30) days prior to such prepayment, and (ii) pays to Agent, for the account of the Lenders in accordance with its respective Pro Rata Share, on the date of such prepayment (A) the outstanding principal plus accrued and unpaid interest with respect to the Term Loan Advances, (B) the Prepayment Premium, (C) the Final Payment and (D) all other sums, if any, that shall have become due and payable with respect to the Term Loan Advances, including Lenders' Expenses and interest at the Default Rate with respect to any past due amounts.

(e) Mandatory Prepayment Upon an Acceleration. If the Term Loan Advances are accelerated by Agent pursuant to Section 9.1 hereof, following the occurrence and during the continuance of an Event of Default, Borrower shall immediately pay to Agent, for the account of the Lenders in accordance with its respective Pro Rata Share, an amount equal to the sum of (i) all outstanding principal plus accrued and unpaid interest with respect to the Term Loan Advances, (ii) the Prepayment Premium, (iii) the Final Payment and (iv) all other sums, if any, that shall have become due and payable with respect to the Term Loan Advances, including Lenders' Expenses and interest at the Default Rate with respect to any past due amounts.

2.3 Payment of Interest on the Credit Extensions.

(a) Interest Rate. Subject to Section 2.3(b), the principal amount outstanding under each Term Loan Advance shall accrue interest at a floating per annum rate equal to the greater of (i) seven and one-half of one percent (7.50%) and (ii) two percent (2.0%) above the Prime Rate, which interest, in each case, shall be payable monthly in accordance with Section 2.3(d) below.

(b) Default Rate. Immediately upon the occurrence and during the continuance of an Event of Default, Obligations shall bear interest at a rate per annum which is five percent (5.0%) above the rate that is otherwise applicable thereto (the "**Default Rate**"). Fees and expenses which are required to be paid by Borrower pursuant to the Loan Documents (including, without limitation, Lenders' Expenses) but are not paid when due shall bear interest until paid at a rate equal to the highest rate applicable to the Obligations. Payment or acceptance of the increased interest rate provided in this Section 2.3(b) is not a permitted alternative to timely payment and shall not constitute a waiver of any Event of Default or otherwise prejudice or limit any rights or remedies of Agent or any Lender.

(c) Adjustment to Interest Rate. Changes to the interest rate of any Credit Extension based on changes to the Prime Rate shall be effective on the effective date of any change to the Prime Rate and to the extent of any such change.

(d) Payment; Interest Computation. Interest is payable monthly on the Payment Date of each month and shall be computed on the basis of a 360-day year for the actual number of days elapsed. In computing interest, (i) all payments received after 12:00 p.m. Eastern time on any day shall be deemed received at the opening of business on the next Business Day, and (ii) the date of the making of any Credit Extension shall be included and the date of payment shall be excluded; provided, however, that if any Credit Extension is repaid on the same day on which it is made, such day shall be included in computing interest on such Credit Extension.

2.4 Fees. Borrower shall pay to Agent:

(a) Final Payment. The Final Payment, when due hereunder, to be shared between the Lenders pursuant to their respective Term Loan Commitment Percentages;

(b) Prepayment Premium. The Prepayment Premium, when due hereunder, to be shared between the Lenders pursuant to their respective Term Loan Commitment Percentages; and

(c) Lenders' Expenses. All Lenders' Expenses (including reasonable attorneys' fees and expenses for documentation and negotiation of this Agreement) incurred through and after the Effective Date, when due (or, if no stated due date, upon demand by Agent).

Unless otherwise provided in this Agreement or in a separate writing by Agent, Borrower shall not be entitled to any credit, rebate, or repayment of any fees earned by Agent or any Lender pursuant to this Agreement notwithstanding any termination of this Agreement or the suspension or termination of any Lender's obligation to make loans and advances hereunder. Agent may deduct amounts owing by Borrower under the clauses of this Section 2.4 pursuant to the terms of Section 2.5(e). Agent shall provide Borrower written notice of deductions made from the Designated Deposit Account pursuant to the terms of the clauses of this Section 2.4.

2.5 Payments; Pro Rata Treatment; Application of Payments; Debit of Accounts.

(a) All payments (including prepayments) to be made by Borrower under any Loan Document shall be made to Agent for the account of Lenders, in immediately available funds in Dollars, without setoff or counterclaim, before 12:00 p.m. Eastern time on the date when due. Agent shall distribute such payments to Lenders in like funds as set forth in Section 2.6. Payments of principal and/or interest received after 12:00 p.m. Eastern time are considered received at the opening of business on the next Business Day. When a payment is due on a day that is not a Business Day, the payment shall be due the next Business Day, and additional fees or interest, as applicable, shall continue to accrue until paid.

(b) Each borrowing by Borrower from Lenders hereunder shall be made according to the respective Term Loan Commitment Percentages of the relevant Lenders.

(c) Except as otherwise provided herein, each payment (including each prepayment) by Borrower on account of principal or interest on the Term Loan Advances shall be applied according to each Lender's Pro Rata Share of the outstanding principal amount of the Term Loan Advances. The amount of each principal prepayment of the Term Loan Advances shall be applied to reduce the then remaining installments of the Term Loan Advances based upon each Pro Rata Share of Term Loan Advances.

(d) Agent has the exclusive right to determine the order and manner in which all payments with respect to the Obligations may be applied. Borrower shall have no right to specify the order or the accounts to which Agent shall allocate or apply any payments required to be made by Borrower to Agent or otherwise received by Agent or any Lender under this Agreement when any such allocation or application is not specified elsewhere in this Agreement.

(e) Agent may debit any of Borrower's deposit accounts, including the Designated Deposit Account, for principal and interest payments or any other amounts Borrower owes Agent or any Lender when due. These debits shall not constitute a set-off.

(f) Unless Agent shall have been notified in writing by Borrower prior to the date of any payment due to be made by Borrower hereunder that Borrower will not make such payment to Agent, Agent may assume that Borrower is making such payment, and Agent may, but shall not be required to, in reliance upon such assumption, make available to Lenders their respective Pro Rata Share of a corresponding payment amount. If such payment is not made to Agent by Borrower within three (3) Business Days after such due date, Agent shall be entitled to recover, on demand, from each Lender to which any amount which was made available pursuant to the preceding sentence, such amount with interest thereon at the rate per annum equal to the daily average Federal Funds Effective Rate. Nothing herein shall be deemed to limit the rights of Agent or any Lender against Borrower.

2.6 Settlement Procedures. If Agent receives any payment for the account of Lenders on or prior to 12:00 p.m. (Eastern time) on any Business Day, Agent shall pay to each applicable Lender such Lender's Pro Rata Share of such payment on such Business Day. If Agent receives any payment for the account of Lenders after 12:00 p.m. (Eastern time) on any Business Day, Agent shall pay to each applicable Lender such Lender's Pro Rata Share of such payment on the next Business Day.

2.7 Withholding. Payments received by Agent from Borrower under this Agreement will be made free and clear of and without deduction for any and all present or future taxes, levies, imposts, duties, deductions, withholdings, assessments, fees or other charges imposed by any Governmental Authority (including any interest, additions to tax or penalties applicable thereto). Specifically, however, if at any time any Governmental Authority,

applicable law, regulation or international agreement requires Borrower to make any withholding or deduction from any such payment or other sum payable hereunder to Agent, Borrower hereby covenants and agrees that the amount due from Borrower with respect to such payment or other sum payable hereunder will be increased to the extent necessary to ensure that, after the making of such required withholding or deduction, Agent receives a net sum equal to the sum which it would have received had no withholding or deduction been required, and Borrower shall pay the full amount withheld or deducted to the relevant Governmental Authority. Borrower will, upon request, furnish Agent with proof reasonably satisfactory to Agent indicating that Borrower has made such withholding payment; provided, however, that Borrower need not make any withholding payment if the amount or validity of such withholding payment is contested in good faith by appropriate and timely proceedings and as to which payment in full is bonded or reserved against by Borrower. The agreements and obligations of Borrower contained in this Section 2.7 shall survive the termination of this Agreement.

3 CONDITIONS OF LOANS

3.1 Conditions Precedent to Initial Credit Extension. Each Lender's obligation to make the initial Credit Extension hereunder is subject to the condition precedent that Agent shall have received, in form and substance satisfactory to Agent and the Lenders, such documents, and completion of such other matters, as Agent may reasonably deem necessary or appropriate, including, without limitation:

(a) duly executed signatures to the Loan Documents;

(b) duly executed original signatures to the Warrant;

(c) Borrower's Operating Documents;

(d) a secretary's corporate borrowing certificate of Borrower with respect to Borrower's Operating Documents, incumbency and resolutions authorizing the execution and delivery of this Agreement and the other Loan Documents to which it is a party;

(e) duly executed signatures to the completed Borrowing Resolutions for Borrower;

(f) certified copies, dated as of a recent date, of financing statement searches, as Agent may request, accompanied by written evidence (including any UCC termination statements) that the Liens indicated in any such financing statements either constitute Permitted Liens or have been or, in connection with the initial Credit Extension, will be terminated or released; and

(g) payment of the fees and Lenders' Expenses then due as specified in Section 2.4 hereof.

3.2 Conditions Precedent to all Credit Extensions. Each Lender's obligation to make each Credit Extension, including the initial Credit Extension, is subject to the following conditions precedent:

(a) timely receipt by the Lenders of (i) an executed Disbursement Letter; and (ii) an executed Payment/Advance Form and any materials and documents required by Section 3.4;

(b) the representations and warranties in this Agreement shall be true, accurate, and complete in all material respects on the date of the Disbursement Letter (and the Payment/Advance Form) and on the Funding Date of each Credit Extension; provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof; and provided, further that those representations and warranties expressly referring to a specific date shall be true, accurate and complete in all material respects as of such date, and no Event of Default shall have occurred and be continuing or result from the Credit Extension. Each Credit Extension is Borrower's representation and warranty on that date that the representations and warranties in this Agreement remain true, accurate, and complete in all material respects; provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof; and provided, further that those representations

and warranties expressly referring to a specific date shall be true, accurate and complete in all material respects as of such date; and

(c) Agent and each Lender determine to its reasonable satisfaction that there has not been any material impairment in the general affairs, management, results of operation, financial condition or the prospect of repayment of the Obligations.

3.3 Covenant to Deliver. Borrower agrees to deliver to Agent and each Lender each item required to be delivered to Agent and each Lender under this Agreement as a condition precedent to any Credit Extension. Borrower expressly agrees that a Credit Extension made prior to the receipt by Agent and each Lender of any such item shall not constitute a waiver by Agent or Lenders of Borrower's obligation to deliver such item, and the making of any Credit Extension in the absence of a required item shall be in each Lender's sole discretion.

3.4 Procedures for Borrowing.

(a) Term Loan Advances. Subject to the prior satisfaction of all other applicable conditions to the making of a Credit Extension set forth in this Agreement, to obtain a Credit Extension, Borrower shall notify Agent (which notice shall be irrevocable) by electronic mail, facsimile, or telephone by 12:00 p.m. Eastern time at least three (3) Business Days before the proposed Funding Date of such Credit Extension. Together with any such electronic or facsimile notification, Borrower shall deliver to Agent by electronic mail or facsimile a completed Disbursement Letter (and Payment/Advance Form) executed by an Authorized Signer. Agent may rely on any telephone notice given by a person whom Agent believes is an Authorized Signer. On the Funding Date, Agent shall credit the Credit Extensions to the Designated Deposit Account. Agent may make Credit Extensions under this Agreement based on instructions from an Authorized Signer or without instructions if the Credit Extensions are necessary to meet Obligations which have become due.

(b) Funding. In determining compliance with any condition hereunder to the making of a Credit Extension that, by its terms, must be fulfilled to the satisfaction of a Lender, Agent may presume that such condition is satisfactory to such Lender unless Agent shall have received notice to the contrary from such Lender prior to the making of such Credit Extension. Unless Agent shall have been notified in writing by any Lender prior to the date of any Credit Extension, that such Lender will not make the amount that would constitute its share of such borrowing available to Agent, Agent may assume that such Lender is making such amount available to Agent, and Agent may, in reliance upon such assumption, make available to Borrower a corresponding amount. If such amount is not made available to Agent by the required time on the Funding Date therefor, such Lender shall pay to Agent, on demand, such amount with interest thereon, at a rate equal to the greater of (i) the Federal Funds Effective Rate or (ii) a rate determined by Agent in accordance with banking industry rules on interbank compensation, for the period until such Lender makes such amount immediately available to Agent. If such Lender's share of such Credit Extension is not made available to Agent by such Lender within five (5) Business Days after such Funding Date, Agent shall also be entitled to recover such amount with interest thereon at the rate per annum applicable to the Term Loan Advances, on demand, from Borrower.

4 CREATION OF SECURITY INTEREST

4.1 Grant of Security Interest. Borrower hereby grants Agent, for the ratable benefit of the Lenders, to secure the payment and performance in full of all of the Obligations, a continuing security interest in, and pledges to Agent, for the ratable benefit of the Lenders, the Collateral, wherever located, whether now owned or hereafter acquired or arising, and all proceeds and products thereof. For clarity, any reference to "Agent's Lien" or any granting of collateral to Agent in this Agreement or any Loan Document means the Lien granted to Agent for the ratable benefit of the Lenders.

Borrower acknowledges that it previously has entered, and/or may in the future enter, into Bank Services Agreements with SVB. Regardless of the terms of any Bank Services Agreement, Borrower agrees that any amounts Borrower owes SVB thereunder shall be deemed to be Obligations hereunder and that it is the intent of Borrower and SVB to have all such Obligations secured by the first priority perfected security interest in the Collateral granted herein (subject only to Permitted Liens that are permitted pursuant to the terms of this Agreement to have superior priority to Agent's Lien in this Agreement).

If this Agreement is terminated, Agent's Lien in the Collateral shall continue until the Obligations (other than inchoate indemnity obligations) are repaid in full in cash. Upon payment in full in cash of the Obligations (other than inchoate indemnity obligations) and at such time as the Lenders' obligation to make Credit Extensions has terminated, Agent shall, at the sole cost and expense of Borrower, release its Liens in the Collateral and all rights therein shall revert to Borrower. In the event (x) all Obligations (other than inchoate indemnity obligations), except for Bank Services, are satisfied in full, and (y) this Agreement is terminated, Agent shall terminate the security interest granted herein upon Borrower providing to SVB cash collateral acceptable to SVB in its good faith business judgment for Bank Services, if any. In the event such Bank Services consist of outstanding Letters of Credit, Borrower shall provide to SVB cash collateral in an amount equal to (x) if such Letters of Credit are denominated in Dollars, then at least one hundred five percent (105.0%); and (y) if such Letters of Credit are denominated in a Foreign Currency, then at least one hundred ten percent (110.0%), of the Dollar Equivalent of the face amount of all such Letters of Credit plus, in each case, all interest, fees, and costs due or to become due in connection therewith (as estimated by SVB in its business judgment), to secure all of the Obligations relating to such Letters of Credit.

4.2 Priority of Security Interest. Borrower represents, warrants, and covenants that the security interests granted herein are and shall at all times continue to be a first priority perfected security interests in the Collateral (subject only to Permitted Liens that are permitted pursuant to the terms of this Agreement to have superior priority to Agent's Lien under this Agreement). If Borrower shall acquire a commercial tort claim, Borrower shall promptly notify Agent in a writing signed by Borrower of the general details thereof and grant to Agent, for the ratable benefit of the Lenders, in such writing a security interest therein and in the proceeds thereof, all upon the terms of this Agreement, with such writing to be in form and substance reasonably satisfactory to Agent.

4.3 Authorization to File Financing Statements. Borrower hereby authorizes Agent, on behalf of the Lenders, to file financing statements, without notice to Borrower, with all appropriate jurisdictions to perfect or protect Agent's and Lenders' interest or rights hereunder, including a notice that any disposition of the Collateral, by either Borrower or any other Person, in violation of this Agreement, shall be deemed to violate the rights of Agent under the Code.

5 REPRESENTATIONS AND WARRANTIES

Borrower represents and warrants as follows:

5.1 Due Organization, Authorization; Power and Authority. Borrower is duly existing and in good standing as a Registered Organization in its jurisdiction of formation and is qualified and licensed to do business and is in good standing in any jurisdiction in which the conduct of its business or its ownership of property requires that it be qualified except where the failure to do so could not reasonably be expected to have a material adverse effect on Borrower's business. Borrower previously delivered to SVB a completed certificate signed by Borrower, entitled "Perfection Certificate" dated as of November 9, 2016, as amended by Schedule 2 to that certain First Amendment to Loan and Security Agreement dated as of November 26, 2018 between Borrower and SVB (as amended, the "**Perfection Certificate**"). Borrower represents and warrants to Agent and each Lender that (a) Borrower's exact legal name is that indicated on the Perfection Certificate and on the signature page hereof; (b) Borrower is an organization of the type and is organized in the jurisdiction set forth in the Perfection Certificate; (c) the Perfection Certificate accurately sets forth Borrower's organizational identification number or accurately states that Borrower has none; (d) the Perfection Certificate accurately sets forth Borrower's place of business, or, if more than one, its chief executive office as well as Borrower's mailing address (if different than its chief executive office); (e) Borrower (and each of its predecessors) has not, in the past five (5) years, changed its jurisdiction of formation, organizational structure or type, or any organizational number assigned by its jurisdiction; and (f) all other information set forth on the Perfection Certificate pertaining to Borrower and each of its Subsidiaries is accurate and complete (it being understood and agreed that Borrower may from time to time update certain information in the Perfection Certificate after the Effective Date to the extent of any notice required or permitted by one or more specific provisions in this Agreement). If Borrower is not now a Registered Organization but later becomes one, Borrower shall promptly notify Agent of such occurrence and provide Agent with Borrower's organizational identification number.

The execution, delivery and performance by Borrower of the Loan Documents to which it is a party have been duly authorized, and do not (i) conflict with any of Borrower's organizational documents, (ii) contravene, conflict with, constitute a default under or violate any material Requirement of Law, (iii) contravene, conflict or violate any

applicable order, writ, judgment, injunction, decree, determination or award of any Governmental Authority by which Borrower or any of its Subsidiaries or any of their property or assets may be bound or affected, (iv) require any action by, filing, registration, or qualification with, or Governmental Approval from, any Governmental Authority (except such Governmental Approvals which have already been obtained and are in full force and effect (or are being obtained pursuant to Section 6.1(b))), or (v) conflict with, contravene, constitute a default or breach under, or result in or permit the termination or acceleration of, any material agreement by which Borrower is bound. Borrower is not in default under any agreement to which it is a party or by which it is bound in which the default could reasonably be expected to have a material adverse effect on Borrower's business.

5.2 Collateral. Borrower has good title to, rights in, and the power to transfer each item of the Collateral upon which it purports to grant a Lien hereunder, free and clear of any and all Liens except Permitted Liens. Borrower has no Collateral Accounts at or with any bank or financial institution other than SVB or SVB's Affiliates except for the Collateral Accounts described in the Perfection Certificate and which Borrower has given Agent notice and taken such actions as are necessary to give Agent, for the ratable benefit of the Lenders, a perfected security interest therein, pursuant to the terms of Section 6.6(b) to the extent required under Section 6.6(b) hereof. The Accounts are bona fide, existing obligations of the Account Debtors.

The Collateral is not in the possession of any third party bailee (such as a warehouse) except as otherwise provided in the Perfection Certificate, locations disclosed to Agent pursuant to Section 7.2, and locations of Experimental Compounds in the ordinary course of business in connection with clinical trials. None of the components of the Collateral shall be maintained at locations other than: (i) locations as provided in the Perfection Certificate, (ii) locations as permitted pursuant to Section 7.2, (iii) locations of mobile equipment, including phones, tablets and computers with employees and consultants in the ordinary course of business, (iv) locations where Collateral may be temporarily located for sales, testing or demonstration purposes in the ordinary course of business, (v) locations where biopharmaceutical compounds and therapeutic materials are located in the ordinary course of business in connection with clinical trials, and (vi) other locations where not more than Fifty Thousand Dollars ($50,000.00) of Collateral in the aggregate may be located at any time.

All Inventory is in all material respects of good and marketable quality, free from material defects, except for Inventory for which adequate reserves have been made in accordance with GAAP. The foregoing representation shall not apply to Inventory consisting Experimental Compounds.

Borrower is the sole owner of the Intellectual Property which it owns or purports to own except for (a) non-exclusive licenses granted to its third parties in the ordinary course of business, (b) over-the-counter software and software that is commercially available to the public, (c) licenses that are disclosed in writing to Agent pursuant to Section 6.7(b), (d) material Intellectual Property licensed to Borrower and noted on the Perfection Certificate, and (e) immaterial Intellectual Property licensed to Borrower in the ordinary course of business. To the best of Borrower's knowledge, each Patent (other than patent applications) which it owns or purports to own and which is material to Borrower's business is valid and enforceable, and no part of the Intellectual Property which Borrower owns or purports to own and which is material to Borrower's business has been judged invalid or unenforceable, in whole or in part. To the best of Borrower's knowledge, no claim has been made that any part of the Intellectual Property violates the rights of any third party except to the extent such claim would not reasonably be expected to have a material adverse effect on Borrower's business.

Except as noted on the Perfection Certificate, Borrower is not a party to, nor is bound by, any Restricted License.

5.3 Litigation. There are no actions or proceedings pending or, to the knowledge of any Responsible Officer, threatened in writing by or against Borrower or any of its Subsidiaries involving more than, individually or in the aggregate, One Hundred Thousand Dollars ($100,000.00).

5.4 Financial Statements; Financial Condition. All consolidated financial statements for Borrower and any of its Subsidiaries delivered to Agent and the Lenders fairly present in all material respects Borrower's consolidated financial condition and Borrower's consolidated results of operations. There has not been any material deterioration in Borrower's consolidated financial condition since the date of the most recent financial statements submitted to Agent and the Lenders.

5.5 Solvency. Borrower is not left with unreasonably small capital after the transactions in this Agreement; and Borrower is able to pay its debts (including trade debts) as they mature.

5.6 Regulatory Compliance. Borrower is not an "investment company" or a company "controlled" by an "investment company" under the Investment Company Act of 1940, as amended. Borrower is not engaged as one of its important activities in extending credit for margin stock (under Regulations X, T and U of the Federal Reserve Board of Governors). Borrower (a) has complied in all material respects with all Requirements of Law, and (b) has not violated any Requirements of Law, in each case where the failure to comply or the violation of which could reasonably be expected to have a material adverse effect on its business. None of Borrower's or any of its Subsidiaries' properties or assets has been used by Borrower or any Subsidiary or, to the best of Borrower's knowledge, by previous Persons, in disposing, producing, storing, treating, or transporting any hazardous substance other than legally. Borrower and each of its Subsidiaries have obtained all consents, approvals and authorizations of, made all declarations or filings with, and given all notices to, all Governmental Authorities that are necessary to continue their respective businesses as currently conducted except where the failure to do so would not reasonably be expected to have a material adverse effect on Borrower's business.

5.7 Subsidiaries; Investments. Borrower does not own any stock, partnership, or other ownership interest or other equity securities except for Permitted Investments.

5.8 Tax Returns and Payments; Pension Contributions. Borrower has timely filed all required tax returns and reports (or appropriate extensions therefor), and Borrower has timely paid all foreign, federal, state and local taxes, assessments, deposits and contributions owed by Borrower except (a) to the extent such taxes are being contested in good faith by appropriate proceedings promptly instituted and diligently conducted, so long as such reserve or other appropriate provision, if any, as shall be required in conformity with GAAP shall have been made therefor, or (b) if such taxes, assessments, deposits and contributions do not, individually or in the aggregate, exceed Twenty-Five Thousand Dollars ($25,000.00).

To the extent Borrower defers payment of any contested taxes, Borrower shall (i) notify Agent in writing of the commencement of, and any material development in, the proceedings, and (ii) post bonds or take any other steps required to prevent the Governmental Authority levying such contested taxes from obtaining a Lien upon any of the Collateral that is other than a "Permitted Lien." Borrower is unaware of any claims or adjustments proposed for any of Borrower's prior tax years which could result in additional taxes becoming due and payable by Borrower in excess of Twenty-Five Thousand Dollars ($25,000.00). Borrower has paid all amounts necessary to fund all present pension, profit sharing and deferred compensation plans in accordance with their terms, and Borrower has not withdrawn from participation in, and has not permitted partial or complete termination of, or permitted the occurrence of any other event with respect to, any such plan which could reasonably be expected to result in any liability of Borrower, including any liability to the Pension Benefit Guaranty Corporation or its successors or any other governmental agency.

5.9 Use of Proceeds. Borrower shall use the proceeds of the Credit Extensions as working capital, to repay the SVB Obligations in full and to fund its general business requirements and not for personal, family, household or agricultural purposes.

5.10 Full Disclosure. No written representation, warranty or other statement of Borrower in any certificate or written statement given to Agent or any Lender, as of the date such representation, warranty, or other statement was made, taken together with all such written certificates and written statements given to Agent or any Lender, contains any untrue statement of a material fact or omits to state a material fact necessary to make the statements contained in the certificates or statements, in light of the circumstances under which they were made, not misleading (it being recognized by Agent and each Lender that the projections and forecasts provided by Borrower in good faith and based upon reasonable assumptions are not viewed as facts and that actual results during the period or periods covered by such projections and forecasts may differ from the projected or forecasted results).

5.11 Definition of "Knowledge." For purposes of the Loan Documents, whenever a representation or warranty is made to Borrower's knowledge or awareness, to the "best of" Borrower's knowledge, or with a similar qualification, knowledge or awareness means the actual knowledge, after reasonable investigation, of any Responsible Officer.

6 AFFIRMATIVE COVENANTS

Borrower shall do all of the following:

6.1 Government Compliance.

(a) Maintain its and all its Subsidiaries' legal existence and good standing in their respective jurisdictions of formation and maintain qualification in each jurisdiction in which the failure to so qualify would reasonably be expected to have a material adverse effect on Borrower's business or operations. Borrower shall comply, and have each Subsidiary comply, in all material respects, with all laws, ordinances and regulations to which it is subject, noncompliance with which could reasonably be expected have a material adverse effect on Borrower's business. Notwithstanding anything to the contrary set forth herein, Borrower's Subsidiaries (which are not a co-borrower or secured guarantor to this Agreement) may wind-up and dissolve to the extent that Borrower determines that it is reasonable to do so and any remaining assets from such Subsidiaries which are not a co-borrower or secured guarantor to this Agreement) are transferred to Borrower or another Subsidiary in accordance with applicable law.

(b) Obtain all of the Governmental Approvals necessary for the performance by Borrower of its obligations under the Loan Documents to which it is a party and the grant of a security interest to Agent in all of the Collateral. Pursuant to the terms of the prior sentence, Borrower shall promptly provide copies of any such obtained Governmental Approvals to Agent.

6.2 Financial Statements, Reports, Certificates. Provide Agent and each Lender with the following:

(a) Monthly Financial Statements. As soon as available, but no later than forty (40) days after the last day of each month, a company prepared consolidated balance sheet and income statement covering Borrower's consolidated operations for such month certified by a Responsible Officer and in a form acceptable to Agent (the "**Monthly Financial Statements**");

(b) Monthly Compliance Certificate. Within forty (40) days after the last day of each month and together with the Monthly Financial Statements, a duly completed Compliance Certificate signed by a Responsible Officer, certifying that as of the end of such month, Borrower was in full compliance with all of the terms and conditions of this Agreement, and such other information as Agent or the Lenders may reasonably request;

(c) Board Projections. As soon as available, at least annually, and in any event no later than within sixty (60) days after the end of each fiscal year of Borrower, and promptly following any material updates or changes thereto, annual Board-approved operating budget and financial projections, in a form acceptable to Agent;

(d) Annual Audited Financial Statements. As soon as available, but no later than one hundred eighty (180) days after the last day of Borrower's fiscal year, audited consolidated financial statements prepared under GAAP, consistently applied, together with an unqualified opinion on the financial statements from an independent certified public accounting firm reasonably acceptable to Agent;

(e) Other Statements. Within five (5) days of delivery, copies of all statements, reports and notices made available to Borrower's security holders or to any holders of Subordinated Debt;

(f) 10-Q Reports, 10-K Reports, and Annual Financial Statements. Within (i) forty-five (45) days after the last day of each fiscal quarter, Borrower's 10-Q report, (ii) ninety (90) days after the last day of Borrower's fiscal year, Borrower's 10-K report, and (iii) ninety (90) days after the last day of Borrower's fiscal year, a company prepared consolidated balance sheet and income statement covering Borrower's consolidated operations for such fiscal year.

(g) SEC Filings. Within five (5) days of filing, copies of all other periodic and other reports, proxy statements and other materials filed by Borrower with the SEC, any Governmental Authority succeeding to any or all of the functions of the SEC or with any national securities exchange, or distributed to its shareholders, as the case may be. Documents required to be delivered pursuant to the terms hereof (to the extent any such documents are

included in materials otherwise filed with the SEC) may be delivered electronically and if so delivered, shall be deemed to have been delivered on the date on which Borrower posts such documents, or provides a link thereto, on Borrower's website on the Internet at Borrower's website address; provided, however, Borrower shall promptly notify Agent in writing (which may be by electronic mail) of the posting of any such documents;

(h) Legal Action Notice. A prompt report of any legal actions pending or threatened in writing against Borrower or any of its Subsidiaries that could reasonably be expected to result in damages or costs to Borrower or any of its Subsidiaries of, individually or in the aggregate, One Hundred Thousand Dollars ($100,000.00) or more;

(i) Beneficial Ownership Information. Prompt written notice of any changes to the beneficial ownership information set out in Section 14 of the Perfection Certificate. Borrower understands and acknowledges that each Lender relies on such true, accurate and up-to-date beneficial ownership information to meet such Lender's regulatory obligations to obtain, verify and record information about the beneficial owners of its legal entity customers; and

(j) Other Financial Information. Other financial information reasonably requested by Agent or any Lender.

6.3 Inventory; Returns. Keep all Inventory in good and marketable condition, free from material defects except for Inventory for which adequate reserves have been made in accordance with GAAP; provided that the foregoing covenant shall not apply to Inventory consisting of Experimental Compounds. Returns and allowances between Borrower and its Account Debtors shall follow Borrower's customary practices as they exist at the Effective Date. Borrower must promptly notify Agent of all returns, recoveries, disputes and claims that involve more than Fifty Thousand Dollars ($50,000.00).

6.4 Taxes; Pensions. Timely file and require each of its Subsidiaries to timely file, all required tax returns and reports (and extensions therefor) and timely pay, and require each of its Subsidiaries to timely pay, all foreign, federal, state and local taxes, assessments, deposits and contributions owed by Borrower and each of its Subsidiaries, except for deferred payment of any taxes contested pursuant to the terms of Section 5.8 hereof, and shall deliver to Agent, on demand, appropriate certificates attesting to such payments, and pay all amounts necessary to fund all present pension, profit sharing and deferred compensation plans in accordance with their terms.

6.5 Insurance.

(a) Keep its business and the Collateral insured for risks and in amounts standard for companies in Borrower's industry and location and as Agent may reasonably request. Insurance policies shall be in a form, with financially sound and reputable insurance companies that are not Affiliates of Borrower, and in amounts that are satisfactory to Agent. All property policies shall have a lender's loss payable endorsement showing Agent as lender loss payee. All liability policies shall show, or have endorsements showing, Agent as an additional insured. Agent shall be named as lender loss payee and/or additional insured with respect to any such insurance providing coverage in respect of any Collateral..

(b) Ensure that proceeds payable under any property policy are, at Agent's option, payable to Agent for the ratable benefit of the Lenders on account of the Obligations. Notwithstanding the foregoing, (i) so long as no Event of Default has occurred and is continuing, Borrower shall have the option of applying the proceeds of any casualty policy up to Two Hundred Fifty Thousand Dollars ($250,000.00) with respect to any loss, but not exceeding Two Hundred Fifty Thousand Dollars ($250,000.00) in the aggregate for all losses under all casualty policies in any one year, toward the replacement or repair of destroyed or damaged property; provided that any such replaced or repaired property (A) shall be of equal or like value as the replaced or repaired Collateral and (B) shall be deemed Collateral in which Agent has been granted a first priority security interest, and (ii) after the occurrence and during the continuance of an Event of Default, all proceeds payable under such casualty policy shall, at the option of the Lenders, be payable to Agent for the ratable benefit of the Lenders on account of the Obligations

(c) At Agent's request, Borrower shall deliver certified copies of insurance policies and evidence of all premium payments. Each provider of any such insurance required under this Section 6.5 shall agree,

by endorsement upon the policy or policies issued by it or by independent instruments furnished to Agent, that it will give Agent thirty (30) days prior written notice before any such policy or policies shall be materially altered or canceled (or ten (10) days prior written notice for cancellation for non-payment of premiums). If Borrower fails to obtain insurance as required under this Section 6.5 or to pay any amount or furnish any required proof of payment to third persons and Agent, Agent may make all or part of such payment or obtain such insurance policies required in this Section 6.5, and take any action under the policies Agent deems prudent.

6.6 Operating Accounts.

(a) Maintain all of its and all of its Subsidiaries' operating, depository and securities accounts with SVB and SVB's Affiliates; provided that, Borrower may maintain one (1) account with CitiBank, so long as such account does not contain more than Ten Thousand Dollars ($10,000.00) in the aggregate any time (the "**CitiBank Account**"). Notwithstanding the foregoing, Australian Subsidiary and Irish Subsidiary may maintain accounts outside of the United States with financial institutions other than SVB and SVB's Affiliates, provided that the maximum aggregate balance in all such accounts shall not exceed One Hundred Fifty Thousand Dollars ($150,000.00) at any time; provided, however, the aggregate balance in such accounts may total up to Three Hundred Thousand Dollars ($300,000.00) for a period not to exceed twenty (20) Business Days during any twelve (12) month period.

(b) Provide Agent five (5) days prior written notice before establishing any Collateral Account at or with any bank or financial institution other than SVB or SVB's Affiliates. For each Collateral Account that Borrower at any time maintains. Borrower shall cause the applicable bank or financial institution (other than SVB) at or with which any Collateral Account is maintained to execute and deliver a Control Agreement or other appropriate instrument with respect to such Collateral Account to perfect Agent's Lien in such Collateral Account in accordance with the terms hereunder which Control Agreement may not be terminated without the prior written consent of the Lenders. The provisions of the previous sentence shall not apply (i) to the CitiBank Account or (ii) to deposit accounts exclusively used for payroll, payroll taxes and other employee wage and benefit payments to or for the benefit of Borrower's employees and identified to Agent and the Lenders by Borrower as such.

6.7 Protection of Intellectual Property Rights.

(a) (i) Use commercially reasonable efforts to protect, defend and maintain the validity and enforceability of its Intellectual Property that is material to its business; (ii) promptly advise Agent in writing of material infringements or any other event that could reasonably be expected to materially and adversely affect the value of its Intellectual Property that is material to its business; and (iii) not allow any Intellectual Property material to Borrower's business to be abandoned, forfeited or dedicated to the public without Agent's written consent.

(b) Provide written notice to Agent within ten (10) days of entering or becoming bound by any Restricted License (other than over-the-counter software and software that is commercially available to the public). Borrower shall take such steps as Agent requests to obtain the consent of, or waiver by, any person whose consent or waiver is necessary for (i) any Restricted License to be deemed "Collateral" and for Agent to have a security interest in it that might otherwise be restricted or prohibited by law or by the terms of any such Restricted License, whether now existing or entered into in the future, and (ii) Agent to have the ability in the event of a liquidation of any Collateral to dispose of such Collateral in accordance with Agent's and the Lenders' rights and remedies under this Agreement and the other Loan Documents.

6.8 Litigation Cooperation. From the date hereof and continuing through the termination of this Agreement, make available to Agent, without expense to Agent or any Lender, Borrower and its officers, employees and agents and Borrower's books and records, to the extent that Agent and/or the Lenders may deem them reasonably necessary to prosecute or defend any third-party suit or proceeding instituted by or against Agent and/or any Lender with respect to any Collateral or relating to Borrower.

6.9 Access to Collateral; Books and Records. Allow Agent, or its agents, at reasonable times, on five (5) Business Day's notice (provided no notice is required if an Event of Default has occurred and is continuing), to inspect the Collateral and audit and copy Borrower' Books. Such inspections or audits shall be conducted no more often than once every twelve (12) months unless an Event of Default has occurred and is continuing, in which case such inspections and audits shall occur as often as Agent shall determine is necessary. The foregoing inspections and

audits shall be at Borrower' expense and the charge therefor shall be One Thousand Dollars ($1,000.00) per person per day (or such higher amount as shall represent Agent's then-current standard charge for the same), plus reasonable out-of-pocket expenses. In the event Borrower and Agent schedule an audit more than eight (8) days in advance, and Borrower cancels or seeks to or reschedules the audit with less than eight (8) days written notice to Agent, then (without limiting any of Agent's or any Lender's rights or remedies) Borrower shall pay Agent a fee of Two Thousand Dollars ($2,000.00 plus any out-of-pocket expenses incurred by Agent to compensate Agent for the anticipated costs and expenses of the cancellation or rescheduling.

6.10 Further Assurances. Execute any further instruments and take further action as Agent and the Lenders reasonably request to perfect or continue Agent's Lien in the Collateral or to effect the purposes of this Agreement. Deliver to Agent and the Lenders, within five (5) days after the same are sent or received, copies of all material correspondence, reports, documents and other filings with any Governmental Authority regarding compliance with or maintenance of Governmental Approvals or Requirements of Law or that could reasonably be expected to have a material adverse effect on any of the Governmental Approvals that are material to its business or otherwise on the operations of Borrower or any of its Subsidiaries.

7 NEGATIVE COVENANTS

Borrower shall not do any of the following without the prior written consent of the Lenders:

7.1 Dispositions. Convey, sell, lease, transfer, assign, or otherwise dispose of (collectively, "**Transfer**"), or permit any of its Subsidiaries to Transfer, all or any part of its business or property, except for Transfers (a) of Inventory in the ordinary course of business; (b) of worn-out or obsolete Equipment that is, in the reasonable judgment of Borrower, no longer economically practicable to maintain or useful in the ordinary course of business of Borrower; (c) consisting of Permitted Liens and Permitted Investments; (d) consisting of the sale or issuance of any stock of Borrower permitted under Section 7.2 of this Agreement; (e) consisting of Borrower's use or transfer of money or Cash Equivalents in a manner that is not prohibited by the terms of this Agreement or the other Loan Documents; and (f) of non-exclusive licenses for the use of the property of Borrower or its Subsidiaries in the ordinary course of business and licenses that could not result in a legal transfer of title of the licensed property but that may be exclusive in respects other than territory and that may be exclusive as to territory only as to discrete geographical areas outside of the United States.

7.2 Changes in Business, Management, Control, or Business Locations. (a) Engage in or permit any of its Subsidiaries to engage in any business other than the businesses currently engaged in by Borrower and such Subsidiary, as applicable, or reasonably related thereto; (b) liquidate or dissolve; (c) fail to provide notice to Agent and Lenders of any Key Person departing from or ceasing to be employed by Borrower within five (5) days after such Key Person's departure from Borrower; or (d) permit or suffer any Change in Control.

Borrower shall not, without at least thirty (30) days prior written notice to Agent: (1) add any new offices or business locations, including warehouses (unless such new offices or business locations contain less than Fifty Thousand Dollars ($50,000.00) in Borrower's assets or property or are clinical locations used in the ordinary course of business for trials of Experimental Compounds) or deliver any portion of the Collateral valued, individually or in the aggregate, in excess of Fifty Thousand Dollars ($50,000.00) to a bailee at a location other than to a bailee and at a location already disclosed in the Perfection Certificate (including clinical locations used in the ordinary course of business for trials of Experimental Compounds), (2) change its jurisdiction of organization, (3) change its organizational structure or type, (4) change its legal name, or (5) change any organizational number (if any) assigned by its jurisdiction of organization. If Borrower intends to add any new offices or business locations, including warehouses, containing in excess of Fifty Thousand Dollars ($50,000.00) of Borrower's assets or property, then Borrower shall cause the landlord of any such new offices or business locations, including warehouses, to execute and deliver a landlord consent in form and substance satisfactory to Agent. If Borrower intends to deliver any portion of the Collateral valued, individually or in the aggregate, in excess of Fifty Thousand Dollars ($50,000.00) to a bailee, and Agent and such bailee are not already parties to a bailee agreement governing both the Collateral and the location to which Borrower intends to deliver the Collateral, then Borrower will first receive the written consent of Agent, and such bailee shall execute and deliver a bailee agreement in form and substance reasonably satisfactory to Agent. The foregoing requirements shall not apply to Experimental Compounds and materials that are located at clinical sites for testing purposes.

7.3 Mergers or Acquisitions. Merge or consolidate, or permit any of its Subsidiaries to merge or consolidate, with any other Person, or acquire, or permit any of its Subsidiaries to acquire, all or substantially all of the capital stock or property of another Person (including, without limitation, by the formation of any Subsidiary). A Subsidiary may merge or consolidate into another Subsidiary or into Borrower.

7.4 Indebtedness. Create, incur, assume, or be liable for any Indebtedness, or permit any Subsidiary to do so, other than Permitted Indebtedness.

7.5 Encumbrance. Create, incur, allow, or suffer any Lien on any of its property, or assign or convey any right to receive income, including the sale of any Accounts, or permit any of its Subsidiaries to do so, except for Permitted Liens, permit any Collateral not to be subject to the first priority security interest granted herein, or enter into any agreement, document, instrument or other arrangement (except with or in favor of Agent, for the ratable benefit of the Lenders) with any Person which directly or indirectly prohibits or has the effect of prohibiting Borrower or any Subsidiary from assigning, mortgaging, pledging, granting a security interest in or upon, or encumbering any of Borrower's or any Subsidiary's Intellectual Property, except as is otherwise permitted in Section 7.1 hereof and the definition of "Permitted Liens" herein.

7.6 Maintenance of Collateral Accounts. Maintain any Collateral Account except pursuant to the terms of Section 6.6(b) hereof.

7.7 Distributions; Investments. (a) Pay any dividends or make any distribution or payment or redeem, retire or purchase any of its capital stock provided that (i) Borrower may convert any of its convertible securities (including warrants and convertible debt) into other securities pursuant to the terms of such convertible securities or otherwise in exchange thereof, (ii) Borrower may pay dividends solely in common stock, and (iii) Borrower may purchase fractional shares of capital stock arising out of stock dividends, splits or combinations, provided such purchases do not exceed Twenty-Five Thousand Dollars ($25,000.00) in the aggregate in any fiscal year; or (b) directly or indirectly make any Investment (including, without limitation, by the formation of any Subsidiary) other than Permitted Investments, or permit any of its Subsidiaries to do so.

7.8 Transactions with Affiliates. Directly or indirectly enter into or permit to exist any material transaction with any Affiliate of Borrower, except for (a) transactions that are in the ordinary course of Borrower's business, upon fair and reasonable terms that are no less favorable to Borrower than would be obtained in an arm's length transaction with a non-affiliated Person, (b) Subordinated Debt and equity investments by Borrower's investors in Borrower, (c) reasonable and customary fees paid to members of Borrower's Board and its Subsidiaries, (d) customary employment arrangements with executive officers, (e) Permitted Investments, (f) transactions with Subsidiaries listed on the Perfection Certificate as of the Effective Date, and (g) transactions permitted under Section 7.7.

7.9 Subordinated Debt. (a) Make or permit any payment on any Subordinated Debt, except under the terms of the subordination, intercreditor, or other similar agreement to which such Subordinated Debt is subject, or (b) amend any provision in any document relating to the Subordinated Debt which would increase the amount thereof, provide for earlier or greater principal, interest, or other payments thereon, or adversely affect the subordination thereof to Obligations owed to Agent and the Lenders.

7.10 Compliance. Become an "investment company" or a company controlled by an "investment company", under the Investment Company Act of 1940, as amended, or undertake as one of its important activities extending credit to purchase or carry margin stock (as defined in Regulation U of the Board of Governors of the Federal Reserve System), or use the proceeds of any Credit Extension for that purpose; fail to (a) meet the minimum funding requirements of ERISA, (b) prevent a Reportable Event or Prohibited Transaction, as defined in ERISA, from occurring, or (c) comply with the Federal Fair Labor Standards Act, the failure of any of the conditions described in clauses (a) through (c) which could reasonably be expected to have a material adverse effect on Borrower's business; or violate any other law or regulation, if the violation could reasonably be expected to have a material adverse effect on Borrower's business, or permit any of its Subsidiaries to do so; withdraw or permit any Subsidiary to withdraw from participation in, permit partial or complete termination of, or permit the occurrence of any other event with respect to, any present pension, profit sharing and deferred compensation plan which could reasonably be expected to

result in any liability of Borrower, including any liability to the Pension Benefit Guaranty Corporation or its successors or any other governmental agency.

8 EVENTS OF DEFAULT

Any one of the following shall constitute an event of default (an "**Event of Default**") under this Agreement:

8.1 Payment Default. Borrower fails to (a) make any payment of principal or interest on any Credit Extension when due, or (b) pay any other Obligations within three (3) Business Days after such Obligations are due and payable (which three (3) Business Day cure period shall not apply to payments due on the Term Loan Maturity Date). During the cure period, the failure to make or pay any payment specified under clause (b) hereunder is not an Event of Default (but no Credit Extension will be made during the cure period);

8.2 Covenant Default.

(a) Borrower fails or neglects to perform any obligation in Sections 6.2, 6.4, 6.5, 6.6, or 6.7(b), or violates any covenant in Section 7; or

(b) Borrower fails or neglects to perform, keep, or observe any other term, provision, condition, covenant or agreement contained in this Agreement or any Loan Documents, and as to any default (other than those specified in this Section 8) under such other term, provision, condition, covenant or agreement that can be cured, has failed to cure the default within ten (10) days after the occurrence thereof; provided, however, that if the default cannot by its nature be cured within the ten (10) day period or cannot after diligent attempts by Borrower be cured within such ten (10) day period, and such default is likely to be cured within a reasonable time, then Borrower shall have an additional period (which shall not in any case exceed thirty (30) days) to attempt to cure such default, and within such reasonable time period the failure to cure the default shall not be deemed an Event of Default (but no Credit Extensions shall be made during such cure period). Cure periods provided under this section shall not apply, among other things, to financial covenants or any other covenants set forth in clause (a) above;

8.3 Material Adverse Change. A Material Adverse Change occurs;

8.4 Attachment; Levy; Restraint on Business.

(a) (i) The service of process seeking to attach, by trustee or similar process, any funds of Borrower or of any entity under the control of Borrower (including a Subsidiary), or (ii) a notice of lien or levy is filed against any of Borrower's assets by any Governmental Authority, and the same under subclauses (i) and (ii) hereof are not, within ten (10) days after the occurrence thereof, discharged or stayed (whether through the posting of a bond or otherwise); provided, however, no Credit Extensions shall be made during any ten (10) day cure period; or

(b) (i) any material portion of Borrower's assets is attached, seized, levied on, or comes into possession of a trustee or receiver, or (ii) any court order enjoins, restrains, or prevents Borrower from conducting all or any material part of its business;

8.5 Insolvency. (a) Borrower is unable to pay its debts (including trade debts) as they become due; (b) Borrower begins an Insolvency Proceeding; or (c) an Insolvency Proceeding is begun against Borrower and is not dismissed or stayed within forty-five (45) days (but no Credit Extensions shall be made while any of the conditions described in clause (a) exist and/or until any Insolvency Proceeding is dismissed);

8.6 Other Agreements. There is, under any agreement to which Borrower is a party with a third party or parties, (a) any default resulting in a right by such third party or parties, whether or not exercised, to accelerate the maturity of any Indebtedness in an amount individually or in the aggregate in excess of One Hundred Thousand Dollars ($100,000.00); or (b) any breach or default by Borrower, the result of which could have a material adverse effect on Borrower's business; provided, however, that the Event of Default under this Section 8.6 caused by the occurrence of a breach or default under such other agreement shall be cured or waived for purposes of this Agreement upon Agent receiving written notice from the party asserting such breach or default of such cure or waiver of the

breach or default under such other agreement, if at the time of such cure or waiver under such other agreement (x) a Lender has not declared an Event of Default under this Agreement and/or exercised any rights with respect thereto; (y) any such cure or waiver does not result in an Event of Default under any other provision of this Agreement or any Loan Document; and (z) in connection with any such cure or waiver under such other agreement, the terms of any agreement with such third party are not modified or amended in any manner which could in the good faith business judgment of Agent be materially less advantageous to Borrower;

8.7 Judgments; Penalties. One or more fines, penalties or final judgments, orders or decrees for the payment of money in an amount, individually or in the aggregate, of at least One Hundred Thousand Dollars ($100,000.00) (not covered by independent third-party insurance as to which liability has been accepted by such insurance carrier) shall be rendered against Borrower by any Governmental Authority, and the same are not, within ten (10) days after the entry, assessment or issuance thereof, discharged, satisfied, or paid, or after execution thereof, stayed or bonded pending appeal, or such judgments are not discharged prior to the expiration of any such stay (provided that no Credit Extensions will be made prior to the satisfaction, payment, discharge, stay, or bonding of such fine, penalty, judgment, order or decree);

8.8 Misrepresentations. Borrower or any Person acting for Borrower makes any representation, warranty, or other statement now or later in this Agreement, any Loan Document or in any writing delivered to Agent or any Lender or to induce Agent or any Lender to enter this Agreement or any Loan Document, and such representation, warranty, or other statement is incorrect in any material respect when made;

8.9 Subordinated Debt. Any document, instrument, or agreement evidencing any Subordinated Debt shall for any reason be revoked or invalidated or otherwise cease to be in full force and effect, any Person shall be in breach thereof or contest in any manner the validity or enforceability thereof or deny that it has any further liability or obligation thereunder, or the Obligations shall for any reason be subordinated or shall not have the priority contemplated by this Agreement; or

8.10 Governmental Approvals. Any Governmental Approval shall have been (a) revoked, rescinded, suspended, modified in an adverse manner or not renewed in the ordinary course for a full term or (b) subject to any decision by a Governmental Authority that designates a hearing with respect to any applications for renewal of any of such Governmental Approval or that could result in the Governmental Authority taking any of the actions described in clause (a) above, and such decision or such revocation, rescission, suspension, modification or non-renewal causes, or could reasonably be expected to cause, a Material Adverse Change.

9 RIGHTS AND REMEDIES

9.1 Rights and Remedies. Upon the occurrence and during the continuance of an Event of Default, Agent, as directed by each Lender in accordance with the Lender Intercreditor Agreement or, if such rights and remedies are not addressed in the Lender Intercreditor Agreement, as directed by a majority of the Lenders, may, without notice or demand, do any or all of the following:

(a) declare all Obligations immediately due and payable (but if an Event of Default described in Section 8.5 occurs all Obligations are immediately due and payable without any action by Agent or any Lender);

(b) stop advancing money or extending credit for Borrower's benefit under this Agreement or under any other agreement among Borrower, Agent, and/or any Lenders;

(c) demand that Borrower (i) deposit cash with SVB in an amount equal to at least (A) one hundred five percent (105.0%) of the Dollar Equivalent of the aggregate face amount of all Letters of Credit denominated in Dollars remaining undrawn, and (B) one hundred ten percent (110.0%) of the Dollar Equivalent of the aggregate face amount of all Letters of Credit denominated in a Foreign Currency remaining undrawn (plus, in each case, all interest, fees, and costs due or to become due in connection therewith (as estimated by SVB in its good faith business judgment)), to secure all of the Obligations relating to such Letters of Credit, as collateral security for the repayment of any future drawings under such Letters of Credit, and Borrower shall forthwith deposit and pay such

amounts, and (ii) pay in advance all letter of credit fees scheduled to be paid or payable over the remaining term of any Letters of Credit;

(d) terminate any FX Contracts;

(e) verify the amount of, demand payment of and performance under, and collect any Accounts and General Intangibles, settle or adjust disputes and claims directly with Account Debtors for amounts on terms and in any order that Agent and/or the Lenders consider advisable, and notify any Person owing Borrower money of Agent's security interest in such funds;

(f) make any payments and do any acts Agent or any Lender considers necessary or reasonable to protect the Collateral and/or its security interest in the Collateral. Borrower shall assemble the Collateral if Agent requests and make it available as Agent designates. Agent may enter premises where the Collateral is located, take and maintain possession of any part of the Collateral, and pay, purchase, contest, or compromise any Lien which appears to be prior or superior to its security interest and pay all expenses incurred. Borrower grants Agent a license to enter and occupy any of its premises, without charge, to exercise any of Agent's rights or remedies;

(g) apply to the Obligations (i) any balances and deposits of Borrower it holds, or (ii) any amount held by Agent owing to or for the credit or the account of Borrower;

(h) ship, reclaim, recover, store, finish, maintain, repair, prepare for sale, advertise for sale, and sell the Collateral. Agent, for the benefit of the Lenders is hereby granted a non-exclusive, royalty-free license or other right to use, without charge, Borrower's labels, Patents, Copyrights, mask works, rights of use of any name, trade secrets, trade names, Trademarks, and advertising matter, or any similar property as it pertains to the Collateral, in completing production of, advertising for sale, and selling any Collateral and, in connection with Agent's exercise of its rights under this Section, Borrower's rights under all licenses and all franchise agreements inure to Agent, for the ratable benefit of the Lenders;

(i) place a "hold" on any account maintained with Agent or Lenders and/or deliver a notice of exclusive control, any entitlement order, or other directions or instructions pursuant to any Control Agreement or similar agreements providing control of any Collateral;

(j) demand and receive possession of Borrower's Books; and

(k) exercise all rights and remedies available to Agent and the Lenders under the Loan Documents or at law or equity, including all remedies provided under the Code (including disposal of the Collateral pursuant to the terms thereof).

9.2 Power of Attorney. Borrower hereby irrevocably appoints Agent, for the benefit of the Lenders, as its lawful attorney-in-fact, exercisable upon the occurrence and during the continuance of an Event of Default, to: (a) endorse Borrower's name on any checks or other forms of payment or security; (b) sign Borrower's name on any invoice or bill of lading for any Account or drafts against Account Debtors; (c) settle and adjust disputes and claims about the Accounts directly with Account Debtors, for amounts and on terms Agent determines reasonable; (d) make, settle, and adjust all claims under Borrower's insurance policies; (e) pay, contest or settle any Lien, charge, encumbrance, security interest, and adverse claim in or to the Collateral, or any judgment based thereon, or otherwise take any action to terminate or discharge the same; and (f) transfer the Collateral into the name of Agent or a third party as the Code permits. Borrower hereby appoints Agent as its lawful attorney-in-fact to sign Borrower's name on any documents necessary to perfect or continue the perfection of Agent's security interest in the Collateral regardless of whether an Event of Default has occurred until all Obligations (other than inchoate indemnity obligations and any other obligations which, by their terms, are to survive the termination of this Agreement) have been satisfied in full and Lenders are under no further obligation to make Credit Extensions hereunder. Agent's foregoing appointment as Borrower's attorney in fact, and all of Agent's rights and powers, coupled with an interest, are irrevocable until all Obligations (other than inchoate indemnity obligations and any other obligations which, by their terms, are to survive

the termination of this Agreement) have been fully repaid and performed and each Lender's obligation to provide Credit Extensions terminates.

9.3 Protective Payments. If Borrower fails to obtain the insurance called for by Section 6.5 or fails to pay any premium thereon or fails to pay any other amount which Borrower is obligated to pay under this Agreement or any other Loan Document or which may be required to preserve the Collateral, Agent may obtain such insurance or make such payment, and all amounts so paid by Agent are Lenders' Expenses and immediately due and payable, bearing interest at the then highest rate applicable to the Obligations, and secured by the Collateral. Agent will make reasonable efforts to provide Borrower with notice of Agent obtaining such insurance at the time it is obtained or within a reasonable time thereafter. No payments by Agent are deemed an agreement to make similar payments in the future or Agent's and/or Lender's waiver of any Event of Default.

9.4 Application of Payments and Proceeds Upon Default. If an Event of Default has occurred and is continuing, Agent shall have the right to apply in any order any funds in its possession, whether from Borrower's account balances, payments, proceeds realized as the result of any collection of Accounts or other disposition of the Collateral, or otherwise, to the Obligations. Agent shall pay any surplus to Borrower by credit to the Designated Deposit Account or to other Persons legally entitled thereto; Borrower shall remain liable to Agent and the Lenders for any deficiency. If Agent, directly or indirectly, enters into a deferred payment or other credit transaction with any purchaser at any sale of Collateral, Agent shall have the option, exercisable at any time, of either reducing the Obligations by the principal amount of the purchase price or deferring the reduction of the Obligations until the actual receipt by Agent of cash therefor.

9.5 Liability for Collateral. So long as Agent and Lenders comply with reasonable banking practices regarding the safekeeping of the Collateral in their possession or under the control of Agent and/or Lenders, Agent and Lenders shall not be liable or responsible for: (a) the safekeeping of the Collateral; (b) any loss or damage to the Collateral; (c) any diminution in the value of the Collateral; or (d) any act or default of any carrier, warehouseman, bailee, or other Person. Borrower bears all risk of loss, damage or destruction of the Collateral.

9.6 No Waiver; Remedies Cumulative. Agent's and any Lender's failure, at any time or times, to require strict performance by Borrower of any provision of this Agreement or any other Loan Document shall not waive, affect, or diminish any right of Agent or any Lender thereafter to demand strict performance and compliance herewith or therewith. No waiver hereunder shall be effective unless signed by the party granting the waiver and then is only effective for the specific instance and purpose for which it is given. Agent's and each Lender's rights and remedies under this Agreement and the other Loan Documents are cumulative. Agent and each Lender have all rights and remedies provided under the Code, by law, or in equity. Agent's or any Lender's exercise of one right or remedy is not an election and shall not preclude Agent or any Lender from exercising any other remedy under this Agreement or any other Loan Document or other remedy available at law or in equity, and Agent's or any Lender's waiver of any Event of Default is not a continuing waiver. Agent's or any Lender's delay in exercising any remedy is not a waiver, election, or acquiescence.

9.7 Demand Waiver. Borrower waives demand, notice of default or dishonor, notice of payment and nonpayment, notice of any default, nonpayment at maturity, release, compromise, settlement, extension, or renewal of accounts, documents, instruments, chattel paper, and guarantees held by Agent on which Borrower is liable.

10 agent

10.1 Appointment and Authority.

(a) Each Lender hereby irrevocably appoints SVB to act on its behalf as Agent hereunder and under the other Loan Documents and authorizes Agent to take such actions on its behalf and to exercise such powers as are delegated to Agent by the terms hereof or thereof, together with such actions and powers as are reasonably incidental thereto.

(b) The provisions of this Section 10 are solely for the benefit of Agent and Lenders, and Borrower shall not have rights as a third party beneficiary of any of such provisions. Notwithstanding any provision

to the contrary elsewhere in this Agreement, Agent shall not have any duties or responsibilities to any Lender or any other Person, except those expressly set forth herein, or any fiduciary relationship with any Lender, and no implied covenants, functions, responsibilities, duties, obligations or liabilities shall be read into this Agreement or any other Loan Document or otherwise exist against Agent.

10.2 Delegation of Duties. Agent may perform any and all of its duties and exercise its rights and powers hereunder or under any other Loan Document by or through any one or more sub-agents appointed by Agent. Agent and any such sub-agent may perform any and all of its duties and exercise its rights and powers by or through their respective Indemnified Persons. The exculpatory provisions of this Section 10.2 shall apply to any such sub-agent and to the Indemnified Persons of Agent and any such sub-agent, and shall apply to their respective activities in connection with the syndication of the credit facilities provided for herein as well as activities as Agent.

10.3 Exculpatory Provisions. Agent shall have no duties or obligations except those expressly set forth herein and in the other Loan Documents. Without limiting the generality of the foregoing, Agent shall not:

(a) be subject to any fiduciary, trust, agency or other similar duties, regardless of whether any Event of Default has occurred and is continuing;

(b) have any duty to take any discretionary action or exercise any discretionary powers, except discretionary rights and powers expressly contemplated hereby or by the other Loan Documents that Agent is required to exercise as directed in writing by the Lenders, as applicable; provided that Agent shall not be required to take any action that, in its opinion or the opinion of its counsel, may expose Agent to liability or that is contrary to any Loan Document or applicable law; and

(c) except as expressly set forth herein and in the other Loan Documents, have any duty to disclose, and Agent shall not be liable for the failure to disclose, any information relating to Borrower or any of its Affiliates that is communicated to or obtained by any Person serving as Agent or any of its Affiliates in any capacity.

Agent shall not be liable for any action taken or not taken by it (i) with the consent or at the request of the Lenders (or as Agent shall believe in good faith shall be necessary, under the circumstances as provided in Section 13.7) or (ii) in the absence of its own gross negligence or willful misconduct.

Agent shall not be responsible for or have any duty to ascertain or inquire into (i) any statement, warranty or representation made in or in connection with this Agreement or any other Loan Document, (ii) the contents of any certificate, report or other document delivered hereunder or thereunder or in connection herewith or therewith, (iii) the performance or observance of any of the covenants, agreements or other terms or conditions set forth herein or therein or the occurrence of any Event of Default, (iv) the validity, enforceability, effectiveness or genuineness of this Agreement, any other Loan Document or any other agreement, instrument or document or (v) the satisfaction of any condition set forth in Section 3 or elsewhere herein, other than to confirm receipt of items expressly required to be delivered to Agent.

10.4 Reliance by Agent. Agent shall be entitled to rely upon, and shall not incur any liability for relying upon, any notice, request, certificate, consent, statement, instrument, document or other writing (including any electronic message, internet or intranet website posting or other distribution) believed by it to be genuine and to have been signed, sent or otherwise authenticated by the proper Person. Agent also may rely upon any statement made to it orally or by telephone and believed by it to have been made by the proper Person, and shall not incur any liability for relying thereon. Agent may consult with legal counsel (who may be counsel for Borrower), independent accountants and other experts selected by it, and shall not be liable for any action taken or not taken by it in accordance with the advice of any such counsel, accountants or experts. In determining compliance with any condition hereunder to the making of a Credit Extension that, by its terms, must be fulfilled to the satisfaction of a Lender, Agent may presume that such condition is satisfactory to such Lender unless Agent shall have received notice to the contrary from such Lender prior to the making of such Credit Extension. Agent shall in all cases be fully protected in acting, or in refraining from acting, under this Agreement and the other Loan Documents in accordance with a request of the Lenders, and such request and any action taken or failure to act pursuant thereto shall be binding upon Lenders and all future holders of the Credit Extensions.

10.5 Notice of Default. Agent shall not be deemed to have knowledge or notice of the occurrence of any Event of Default (except with respect to defaults in the payment of principal, interest or fees required to be paid to Agent for the account of Lenders), unless Agent has received notice from a Lender or Borrower referring to this Agreement, describing such Event of Default and stating that such notice is a "notice of default". In the event that Agent receives such a notice, Agent shall give notice thereof to Lenders. Agent shall take such action with respect to such Event of Default as shall be reasonably directed by the Lenders.

10.6 Non-Reliance on Agent and Other Lenders. Each Lender expressly acknowledges that neither Agent nor any of its officers, directors, employees, agents, attorneys in fact or affiliates has made any representations or warranties to it and that no act by Agent hereafter taken, including any review of the affairs of a Group Member or any Affiliate of a Group Member, shall be deemed to constitute any representation or warranty by Agent to any Lender. Each Lender represents to Agent that it has, independently and without reliance upon Agent or any other Lender, and based on such documents and information as it has deemed appropriate, made its own appraisal of, and investigation into, the business, operations, property, financial and other condition and creditworthiness of the Group Members and their Affiliates and made its own decision to make its Credit Extensions hereunder and enter into this Agreement. Each Lender also represents that it will, independently and without reliance upon Agent or any other Lender, and based on such documents and information as it shall deem appropriate at the time, continue to make its own credit analysis, appraisals and decisions in taking or not taking action under this Agreement and the other Loan Documents, and to make such investigation as it deems necessary to inform itself as to the business, operations, property, financial and other condition and creditworthiness of the Group Members and their Affiliates. Except for notices, reports and other documents expressly required to be furnished to Lenders by Agent hereunder, Agent shall have no duty or responsibility to provide any Lender with any credit or other information concerning the business, operations, property, condition (financial or otherwise), prospects or creditworthiness of any Group Member or any Affiliate of a Group Member that may come into the possession of Agent or any of its officers, directors, employees, agents, attorneys in fact or Affiliates.

10.7 Indemnification. Each Lender agrees to indemnify Agent in its capacity as such (to the extent not reimbursed by Borrower and without limiting the obligation of Borrower to do so in accordance with the terms hereof, according to its Term Loan Commitment Percentage in effect on the date on which indemnification is sought under this Section 10.7 (or, if indemnification is sought after the date upon which the Commitments shall have terminated and the Obligations shall have been paid in full, in accordance with its Term Loan Commitment Percentage immediately prior to such date), from and against any and all liabilities, obligations, losses, damages, penalties, actions, judgments, suits, costs, expenses or disbursements of any kind whatsoever that may at any time (whether before or after the payment of the Credit Extensions) be imposed on, incurred by or asserted against Agent in any way relating to or arising out of, the Commitments, this Agreement, any of the other Loan Documents or any documents contemplated by or referred to herein or therein or the transactions contemplated hereby or thereby or any action taken or omitted by Agent under or in connection with any of the foregoing; provided that no Lender shall be liable for the payment of any portion of such liabilities, obligations, losses, damages, penalties, actions, judgments, suits, costs, expenses or disbursements that are found by a final and nonappealable decision of a court of competent jurisdiction to have resulted primarily from Agent's gross negligence or willful misconduct. The agreements in this Section shall survive the payment of the Credit Extensions and all other amounts payable hereunder.

10.8 Agent in Its Individual Capacity. The Person serving as Agent hereunder shall have the same rights and powers in its capacity as a Lender as any other Lender and may exercise the same as though it were not Agent and the term "Lender" or "Lenders" shall, unless otherwise expressly indicated or unless the context otherwise requires, include each such Person serving as Agent hereunder in its individual capacity. Such Person and its Affiliates may accept deposits from, lend money to, act as the financial advisor or in any other advisory capacity for and generally engage in any kind of business with Borrower, any Guarantor or any Subsidiary or other Affiliate thereof as if such Person were not Agent hereunder and without any duty to account therefor to Lenders.

10.9 Successor Agent. Agent may at any time give notice of its resignation to Lenders and Borrower, which resignation shall not be effective until the time at which the majority of the Lenders have delivered to Agent their written consent to such resignation. Upon receipt of any such notice of resignation, the Lenders shall have the right, in consultation with Borrower, to appoint a successor, which shall be a financial institution with an office in the State of California, or an Affiliate of any such bank with an office in the State of California. If no such successor shall have been so appointed by the Lenders and shall have accepted such appointment within thirty (30) days after the

retiring Agent has received the written consent of the majority of the Lenders to such resignation, then the retiring Agent may on behalf of Lenders, appoint a successor Agent meeting the qualifications set forth above; provided that in no event shall any such successor Agent be a Defaulting Lender and provided further that if the retiring Agent shall notify Borrower and Lenders that no qualifying Person has accepted such appointment, then such resignation shall nonetheless become effective in accordance with such notice and (1) the retiring Agent shall be discharged from its duties and obligations hereunder and under the other Loan Documents (except that in the case of any collateral security held by Agent on behalf of the Lenders under any of the Loan Documents, the retiring Agent shall continue to hold such collateral security until such time as a successor Agent is appointed and such collateral security is assigned to such successor Agent) and (2) all payments, communications and determinations provided to be made by, to or through Agent shall instead be made by or to each Lender directly, until such time as the Lenders appoint a successor Agent as provided for above in this Section 10.9. Upon the acceptance of a successor's appointment as Agent hereunder, such successor shall succeed to and become vested with all of the rights, powers, privileges and duties of the retiring (or retired) Agent, and the retiring Agent shall be discharged from all of its duties and obligations hereunder or under the other Loan Documents (if not already discharged therefrom as provided above in this Section 10.9). The fees payable by Borrower to a successor Agent shall be the same as those payable to its predecessor unless otherwise agreed between the Borrower and such successor. After the retiring Agent's resignation hereunder and under the other Loan Documents, the provisions of this Section 10 shall continue in effect for the benefit of such retiring Agent, its sub-agents and their respective Indemnified Persons in respect of any actions taken or omitted to be taken by any of them while the retiring Agent was acting as Agent.

10.10 Defaulting Lender.

(a) Defaulting Lender Adjustments. Notwithstanding anything to the contrary contained in this Agreement, if any Lender becomes a Defaulting Lender, then, until such time as such Lender is no longer a Defaulting Lender, to the extent permitted by applicable law:

(i) Waivers and Amendments. Such Defaulting Lender's right to approve or disapprove any amendment, waiver or consent with respect to this Agreement shall be restricted as long as said Lender is a Defaulting Lender.

(ii) Defaulting Lender Waterfall. Any payment of principal, interest, fees or other amounts received by the Agent for the account of such Defaulting Lender (whether voluntary or mandatory, at maturity, pursuant to Section 8 or otherwise, and including any amounts made available to the Agent by such Defaulting Lender pursuant to Section 13.10), shall be applied at such time or times as may be determined by the Agent as follows: first, to the payment of any amounts owing by such Defaulting Lender to the Agent hereunder; second, as the Borrower may request (so long as no Event of Default exists), to the funding of any Term Loan Advance in respect of which such Defaulting Lender has failed to fund its portion thereof as required by this Agreement, as determined by the Agent; third, if so determined by the Agent and Borrower, to be held in a Deposit Account and released pro rata to satisfy such Defaulting Lender's potential future funding obligations with respect to Term Loan Advances under this Agreement; fourth, so long as no Event of Default has occurred and is continuing, to the payment of any amounts owing to the Borrower as a result of any judgment of a court of competent jurisdiction obtained by the Borrower against such Defaulting Lender as a result of such Defaulting Lender's breach of its obligations under this Agreement; and fifth, to such Defaulting Lender or as otherwise directed by a court of competent jurisdiction; provided that if (A) such payment is a payment of the principal amount of any Term Loan Advances in respect of which such Defaulting Lender has not fully funded its appropriate share and (B) such Term Loan Advances were made at a time when the conditions set forth in Section 3.1 were satisfied or waived, such payment shall be applied solely to pay the Loans of all non-Defaulting Lenders on a *pro rata* basis prior to being applied to the payment of any Term Loan Advances of such Defaulting Lender until such time as all Term Loan Advances are held by the Lenders pro rata in accordance with the Term Loan Commitments under this Agreement. Any payments, prepayments or other amounts paid or payable to a Defaulting Lender that are applied (or held) to pay amounts owed by a Defaulting Lender pursuant to

this Section 10.10(a)(ii) shall be deemed paid to and redirected by such Defaulting Lender, and each Lender irrevocably consents hereto.

(iii) Certain Fees. No Defaulting Lender shall be entitled to receive any fee pursuant to Section 2.4(a) or Section 2.4(b) for any period during which such Lender is a Defaulting Lender (and the Borrower shall not be required to pay any such fee that otherwise would have been required to have been paid to such Defaulting Lender).

(b) Defaulting Lender Cure. If Borrower and Agent agree in writing that a Lender is no longer a Defaulting Lender, Agent will so notify the parties hereto, whereupon as of the effective date specified in such notice and subject to any conditions set forth therein, such Lender will, to the extent applicable, purchase at par that portion of outstanding Term Loan Advances of the other Lenders or take such other actions as Agent may determine to be necessary to cause the Term Loan Advances to be held on a *pro rata* basis by the Lenders in accordance with their respective Term Loan Commitment Percentages, whereupon such Lender will cease to be a Defaulting Lender; provided that no adjustments will be made retroactively with respect to fees accrued or payments made by or on behalf of Borrower while such Lender was a Defaulting Lender; and provided further that, except to the extent otherwise expressly agreed by the affected parties, no change hereunder from Defaulting Lender to Lender will constitute a waiver or release of any claim of any party hereunder arising from such Lender having been a Defaulting Lender.

(c) Termination of Defaulting Lender. The Borrower may terminate the unused amount of the Term Loan Commitment of any Lender that is a Defaulting Lender upon not less than ten (10) Business Days' prior notice to Agent (which shall promptly notify the Lenders thereof), and in such event the provisions of Section 10.10(a)(ii) will apply to all amounts thereafter paid by Borrower for the account of such Defaulting Lender under this Agreement (whether on account of principal, interest, fees, indemnity or other amounts); provided that (i) no Event of Default shall have occurred and be continuing, and (ii) such termination shall not be deemed to be a waiver or release of any claim Borrower, Agent or any Lender may have against such Defaulting Lender.

(d) If the Person serving as Agent is a Defaulting Lender pursuant to clause (d) of the definition thereof, the non-Defaulting Lenders may, to the extent permitted by applicable law, by notice in writing to Borrower and such Person, remove such Person as Agent and, in consultation with Borrower, appoint a successor. If no such successor shall have been so appointed by the non-Defaulting Lenders and shall have accepted such appointment within thirty (30) days (or such earlier day as shall be agreed by the non-Defaulting Lenders) (the "**Removal Effective Date**"), then such removal shall nonetheless become effective in accordance with such notice on the Removal Effective Date.

11 NOTICES

All notices, consents, requests, approvals, demands, or other communication by any party to this Agreement or any other Loan Document must be in writing and shall be deemed to have been validly served, given, or delivered: (a) upon the earlier of actual receipt and three (3) Business Days after deposit in the U.S. mail, first class, registered or certified mail return receipt requested, with proper postage prepaid; (b) upon transmission, when sent by electronic mail or facsimile transmission; (c) one (1) Business Day after deposit with a reputable overnight courier with all charges prepaid; or (d) when delivered, if hand-delivered by messenger, all of which shall be addressed to the party to be notified and sent to the address, facsimile number, or email address indicated below. Agent or Borrower may change its mailing or electronic mail address or facsimile number by giving the other party written notice thereof in accordance with the terms of this Section 11.

If to Borrower: Axsome Therapeutics, Inc.
25 Broadway, 9th Floor
New York, New York 10004
Attn: Chief Executive Officer
Phone: (212) 332-3241
Fax: (212) 320-0245
Email: htabuteau@axsome.com

with a copy to:DLA Piper LLP (US)

2000 University Avenue
East Palo Alto, CA 94303
Attn: Michael Standlee, Esquire
Fax: (650) 687-1199
Email: michael.standlee@dlapiper.com

If to Agent or SVB: Silicon Valley Bank
275 Grove Street, Suite 2-200
Newton, Massachusetts 02466
Attn: Lauren Cole
Email: lcole@svb.com

with a copy to: Morrison & Foerster LLP
200 Clarendon Street, 20th Floor
Boston, Massachusetts 02116
Attn: David A. Ephraim, Esquire
Email: DEphraim@mofo.com

If to WestRiver: WestRiver Innovation Lending Fund VIII, L.P.

c/o WestRiver Management, LLC

3720 Carillon Point

Kirkland, Washington 98033-7455

Attn: Trent Dawson

Email: tdawson@westrivermgmt.com

12 CHOICE OF LAW, VENUE, AND JURY TRIAL WAIVER

Except as otherwise expressly provided in any of the Loan Documents, Massachusetts law governs the Loan Documents without regard to principles of conflicts of law. Borrower, Agent, and Lenders each submit to the exclusive jurisdiction of the State and Federal courts in Boston, Massachusetts; provided, however, that nothing in this Agreement shall be deemed to operate to preclude Agent or Lenders from bringing suit or taking other legal action in any other jurisdiction to realize on the Collateral or any other security for the Obligations, or to enforce a judgment or other court order in favor of Agent or any Lender. Borrower expressly submits and consents in advance to such jurisdiction in any action or suit commenced in any such court, and Borrower hereby waives any objection that it may have based upon lack of personal jurisdiction, improper venue, or forum non conveniens and hereby consents to the granting of such legal or equitable relief as is deemed appropriate by such court. Borrower hereby waives personal service of the summons, complaints, and other process issued in such action or suit and agrees that service of such summons, complaints, and other process may be made by registered or certified mail addressed to Borrower at the address set forth in, or subsequently provided by Borrower in accordance with, Section 11 of this Agreement and that service so made shall be deemed completed upon the earlier to occur of Borrower's actual receipt thereof or three (3) days after deposit in the U.S. mails, proper postage prepaid.

TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, BORROWER, AGENT AND EACH LENDER EACH WAIVE THEIR RIGHT TO A JURY TRIAL OF ANY CLAIM OR CAUSE OF ACTION ARISING OUT OF OR BASED UPON THIS AGREEMENT, THE LOAN DOCUMENTS OR ANY CONTEMPLATED TRANSACTION, INCLUDING CONTRACT, TORT, BREACH OF DUTY AND ALL OTHER CLAIMS. THIS WAIVER IS A MATERIAL INDUCEMENT FOR ALL PARTIES TO ENTER INTO THIS AGREEMENT. EACH PARTY HAS REVIEWED THIS WAIVER WITH ITS COUNSEL.

This Section 12 shall survive the termination of this Agreement.

13 GENERAL PROVISIONS

13.1 Termination Prior to Term Loan Maturity Date; Survival. All covenants, representations and warranties made in this Agreement continue in full force until this Agreement has terminated pursuant to its terms and

all Obligations (other than inchoate indemnity obligations and any other obligations which, by their terms, are to survive the termination of this Agreement) have been satisfied. So long as Borrower has satisfied the Obligations (other than inchoate indemnity obligations, any other obligations which, by their terms, are to survive the termination of this Agreement, and any Obligations under Bank Services Agreements that are cash collateralized in accordance with Section 4.1 of this Agreement), this Agreement may be terminated prior to the Term Loan Maturity Date by Borrower, effective three (3) Business Days after written notice of termination is given to Agent. Those obligations that are expressly specified in this Agreement as surviving this Agreement's termination shall continue to survive notwithstanding this Agreement's termination. Those Obligations that are expressly specified in this Agreement as surviving this Agreement's termination shall continue to survive notwithstanding this Agreement's termination and payment in full of the Obligations then outstanding.

13.2 Successors and Assigns. This Agreement binds and is for the benefit of the successors and permitted assigns of each party. Borrower may not assign this Agreement or any rights or obligations under it without Agent and Lenders' prior written consent (which may be granted or withheld in Agent's and Lenders' discretion). Agent and each Lender has the right, without the consent of or notice to Borrower, to sell, transfer, assign, negotiate, or grant participation in all or any part of, or any interest in, such Lender's obligations, rights, and benefits under this Agreement and the other Loan Documents (other than the Warrant, as to which assignment, transfer and other such actions are governed by the terms thereof).

13.3 Indemnification. Borrower agrees to indemnify, defend and hold Agent, each Lender and their respective directors, officers, employees, agents, attorneys, or any other Person affiliated with or representing Agent or any Lender (each, an "**Indemnified Person**") harmless against: (i) all obligations, demands, claims, and liabilities (collectively, "**Claims**") claimed or asserted by any other party in connection with the transactions contemplated by the Loan Documents; and (ii) all losses or expenses (including Lenders' Expenses) in any way suffered, incurred, or paid by such Indemnified Person as a result of, following from, consequential to, or arising from transactions between Agent, Lenders and Borrower (including reasonable attorneys' fees and expenses), except for Claims and/or losses directly caused by such Indemnified Person's gross negligence or willful misconduct.

This Section 13.3 shall survive until all statutes of limitation with respect to the Claims, losses, and expenses for which indemnity is given shall have run.

13.4 Time of Essence. Time is of the essence for the performance of all Obligations in this Agreement.

13.5 Severability of Provisions. Each provision of this Agreement is severable from every other provision in determining the enforceability of any provision.

13.6 Correction of Loan Documents. Agent may correct patent errors and fill in any blanks in the Loan Documents consistent with the agreement of the parties so long as Agent provides Borrower with written notice of such correction and allows Borrower at least ten (10) days to object to such correction. In the event of such objection, such correction shall not be made except by an amendment signed by both Agent and Borrower.

13.7 Amendments in Writing; Waiver; Integration. No purported amendment or modification of any Loan Document, or waiver, discharge or termination of any obligation under any Loan Document, or release, or subordinate Lenders' security interest in, or consent to the transfer of, any Collateral shall be enforceable or admissible unless, and only to the extent, expressly set forth in a writing signed by Agent, with the consent of the Lenders in accordance with the Lender Intercreditor Agreement or, if such item is not addressed in the Lender Intercreditor Agreement, as consented to by a majority of the Lenders, and Borrower. Without limiting the generality of the foregoing, no oral promise or statement, nor any action, inaction, delay, failure to require performance or course of conduct shall operate as, or evidence, an amendment, supplement or waiver or have any other effect on any Loan Document. Any waiver granted shall be limited to the specific circumstance expressly described in it, and shall not apply to any subsequent or other circumstance, whether similar or dissimilar, or give rise to, or evidence, any obligation or commitment to grant any further waiver. The Loan Documents represent the entire agreement about this subject matter and supersede prior negotiations or agreements. All prior agreements, understandings, representations, warranties, and negotiations between the parties about the subject matter of the Loan Documents merge into the Loan Documents. In the event any provision of any other Loan Document is inconsistent with the provisions of this Agreement, the provisions of this Agreement shall exclusively control.

13.8 Counterparts. This Agreement may be executed in any number of counterparts and by different parties on separate counterparts, each of which, when executed and delivered, is an original, and all taken together, constitute one Agreement.

13.9 Confidentiality Agent and each Lender agree to maintain the confidentiality of Information (as defined below), except that Information may be disclosed (a) to Agent and/or any Lender's subsidiaries or Affiliates, and their respective employees, directors, investors, potential investors, agents, attorneys, accountants and other professional advisors (collectively, "**Representatives**" and, together with Agent and the Lenders, collectively, "**Lender Entities**"); (b) to prospective transferees, assignees, credit providers or purchasers of any of the Lenders' or Agent's interests under or in connection with this Agreement and their Representatives (provided, however, Agent and the Lenders shall use their best efforts to obtain any such prospective transferee's, assignee's, credit provider's, purchaser's or their Representatives' agreement to the terms of this provision); (c) as required by law, regulation, subpoena, or other order; (d) to Agent's or any Lender's regulators or as otherwise required in connection with Agent's or any Lender's examination or audit; (e) as Agent or any Lender considers appropriate in exercising remedies under the Loan Documents; and (f) to third-party service providers of Agent and/or the Lenders so long as such service providers have executed a confidentiality agreement with Agent or the Lenders, as applicable, with terms no less restrictive than those contained herein. The term "Information" means all information received from Borrower regarding Borrower or its business, in each case other than information that is either: (i) in the public domain or in Agent's or any Lender's possession when disclosed to Agent or such Lender, or becomes part of the public domain (other than as a result of its disclosure by Agent or a Lender in violation of this Agreement) after disclosure to Agent and/or the Lenders; or (ii) disclosed to Agent and/or the Lenders by a third party, if Agent/the Lenders do not know that the third party is prohibited from disclosing the information.

Lender Entities may use anonymous forms of confidential information for aggregate datasets, for analyses or reporting, and for any other uses not expressly prohibited in writing by Borrower. The provisions of this Section 13.9 shall survive the termination of this Agreement.

13.10 Right of Setoff. Borrower hereby grants to Agent, for the ratable benefit of the Lenders a Lien and a right of setoff as security for all Obligations to Agent and the Lenders, whether now existing or hereafter arising upon and against all deposits, credits, collateral and property, now or hereafter in the possession, custody, safekeeping or control of Agent or any entity under the control of Agent (including a subsidiary of Agent) in transit to any of them. At any time after the occurrence and during the continuance of an Event of Default, without demand or notice, Agent or any Lender may setoff the same or any part thereof and apply the same to any liability or Obligation of Borrower even though unmatured and regardless of the adequacy of any other collateral securing the Obligations. ANY AND ALL RIGHTS TO REQUIRE AGENT OR ANY LENDER TO EXERCISE ITS RIGHTS OR REMEDIES WITH RESPECT TO ANY OTHER COLLATERAL WHICH SECURES THE OBLIGATIONS, PRIOR TO EXERCISING ITS RIGHT OF SETOFF WITH RESPECT TO SUCH DEPOSITS, CREDITS OR OTHER PROPERTY OF BORROWER, ARE HEREBY KNOWINGLY, VOLUNTARILY AND IRREVOCABLY WAIVED.

13.11 Electronic Execution of Documents. The words "execution," "signed," "signature" and words of like import in any Loan Document shall be deemed to include electronic signatures or the keeping of records in electronic form, each of which shall be of the same legal effect, validity and enforceability as a manually executed signature or the use of a paper-based recordkeeping systems, as the case may be, to the extent and as provided for in any applicable law, including, without limitation, any state law based on the Uniform Electronic Transactions Act.

13.12 Captions. The headings used in this Agreement are for convenience only and shall not affect the interpretation of this Agreement.

13.13 Construction of Agreement. The parties mutually acknowledge that they and their attorneys have participated in the preparation and negotiation of this Agreement. In cases of uncertainty this Agreement shall be construed without regard to which of the parties caused the uncertainty to exist.

13.14 Relationship. The relationship of the parties to this Agreement is determined solely by the provisions of this Agreement. The parties do not intend to create any agency, partnership, joint venture, trust, fiduciary or other relationship with duties or incidents different from those of parties to an arm's-length contract.

13.15 Third Parties. Nothing in this Agreement, whether express or implied, is intended to: (a) confer any benefits, rights or remedies under or by reason of this Agreement on any persons other than the express parties to it and their respective permitted successors and assigns; (b) relieve or discharge the obligation or liability of any person not an express party to this Agreement; or (c) give any person not an express party to this Agreement any right of subrogation or action against any party to this Agreement.

13.16 Patriot Act. Each Lender hereby notifies Borrower that pursuant to the requirements of the USA PATRIOT Act, it is required to obtain, verify and record information that identifies Borrower and each of its Subsidiaries, which information includes the names and addresses of each Borrower and each of its Subsidiaries and other information that will allow Lender, as applicable, to identify Borrower and each of its Subsidiaries in accordance with the USA PATRIOT Act.

13.17 Ratification of Perfection Certificate. Borrower hereby ratifies, confirms and reaffirms, all and singular, the terms and disclosures contained in the Perfection Certificate and acknowledges, confirms and agrees the disclosures and information Borrower provided to SVB in the Perfection Certificate have not changed, as of the Effective Date.

14 DEFINITIONS

14.1 Definitions. As used in the Loan Documents, the word "shall" is mandatory, the word "may" is permissive, the word "or" is not exclusive, the words "includes" and "including" are not limiting, the singular includes the plural, and numbers denoting amounts that are set off in brackets are negative. As used in this Agreement, the following capitalized terms have the following meanings:

"**Account**" is any "**account**" as defined in the Code with such additions to such term as may hereafter be made, and includes, without limitation, all accounts receivable and other sums owing to Borrower.

"**Account Debtor**" is any "**account debtor**" as defined in the Code with such additions to such term as may hereafter be made.

"**Affiliate**" is, with respect to any Person, each other Person that owns or controls directly or indirectly the Person, any Person that controls or is controlled by or is under common control with the Person, and each of that Person's senior executive officers, directors, partners and, for any Person that is a limited liability company, that Person's managers and members.

"**Agent**" is defined in the preamble hereof.

"**Agreement**" is defined in the preamble hereof.

"**Authorized Signer**" is any individual listed in Borrower's Borrowing Resolution who is authorized to execute the Loan Documents, including making (and executing if applicable) any Credit Extension request, on behalf of Borrower.

"**Australian Subsidiary**" is Axsome Therapeutics Australia Pty Ltd, a company organized under the laws of Australia.

"**AXS-12**" means Borrower's AXS-12 product candidate for the treatment of narcolepsy.

"**Bank Services**" are any products, credit services, and/or financial accommodations previously, now, or hereafter provided to Borrower or any of its Subsidiaries by SVB or any SVB Affiliate, including, without limitation, any letters of credit, cash management services (including, without limitation, merchant services, direct deposit of payroll, business credit cards, and check cashing services), interest rate swap arrangements, and foreign exchange services as any such products or services may be identified in SVB's various agreements related thereto (each, a "**Bank Services Agreement**").

"**Bank Services Agreement**" is defined in the definition of Bank Services.

"**Board**" means Borrower's board of directors.

"**Borrower**" is defined in the preamble hereof.

"**Borrower's Books**" are all Borrower's books and records including ledgers, federal and state tax returns, records regarding Borrower's assets or liabilities, the Collateral, business operations or financial condition, and all computer programs or storage or any equipment containing such information.

"**Borrowing Resolutions**" are, with respect to any Person, those resolutions adopted by such Person's board of directors (and, if required under the terms of such Person's Operating Documents, stockholders) and delivered by such Person to Agent approving the Loan Documents to which such Person is a party and the transactions contemplated thereby, together with a certificate executed by its secretary on behalf of such Person certifying (a) such Person has the authority to execute, deliver, and perform its obligations under each of the Loan Documents to which it is a party, (b) that set forth as a part of or attached as an exhibit to such certificate is a true, correct, and complete copy of the resolutions then in full force and effect authorizing and ratifying the execution, delivery, and performance by such Person of the Loan Documents to which it is a party, (c) the name(s) of the Person(s) authorized to execute the Loan Documents, including making (and executing if applicable) any Credit Extension request, on behalf of such Person, together with a sample of the true signature(s) of such Person(s), and (d) that Agent and the Lenders may conclusively rely on such certificate unless and until such Person shall have delivered to Agent and the Lenders a further certificate canceling or amending such prior certificate.

"**Business Day**" is any day that is not a Saturday, Sunday or a day on which Agent is closed.

"**Cash Equivalents**" means (a) marketable direct obligations issued or unconditionally guaranteed by the United States or any agency or any State thereof having maturities of not more than one (1) year from the date of acquisition; (b) commercial paper maturing no more than one (1) year after its creation and having the highest rating from either Standard & Poor's Ratings Group or Moody's Investors Service, Inc.; and (c) SVB's certificates of deposit issued maturing no more than one (1) year after issue.

"**Change in Control**" means (a) at any time, any "person" or "group" (as such terms are used in Sections 13(d) and 14(d) of the Exchange Act), shall become, or obtain rights (whether by means of warrants, options or otherwise) to become, the "beneficial owner" (as defined in Rules 13(d)-3 and 13(d)-5 under the Exchange Act), directly or indirectly, of forty percent (40.0%) or more of the ordinary voting power for the election of directors of Borrower (determined on a fully diluted basis) other than by the sale of Borrower's equity securities in a public offering or to venture capital or private equity investors so long as Borrower identifies to the Agent and the Lenders the venture capital or private equity investors at least seven (7) Business Days prior to the closing of the transaction and provides to Agent and the Lenders a description of the material terms of the transaction; (b) during any period of twelve (12) consecutive months, a majority of the members of the board of directors or other equivalent governing body of Borrower cease to be composed of individuals (i) who were members of that board or equivalent governing body on the first day of such period, (ii) whose election or nomination to that board or equivalent governing body was approved by individuals referred to in clause (i) above constituting at the time of such election or nomination at least a majority of that board or equivalent governing body or (iii) whose election or nomination to that board or other equivalent governing body was approved by individuals referred to in clauses (i) and (ii) above constituting at the time of such election or nomination at least a majority of that board or equivalent governing body; or (c) at any time, Borrower shall cease to own and control, of record and beneficially, directly or indirectly, one hundred percent (100.0%) of each class of outstanding capital stock of each Subsidiary of Borrower free and clear of all Liens (except Liens created by this Agreement).

"**CitiBank Account**" is defined in Section 6.6(a).

"**Claims**" is defined in Section 13.3.

"**Code**" is the Uniform Commercial Code, as the same may, from time to time, be enacted and in effect in the Commonwealth of Massachusetts; provided, that, to the extent that the Code is used to define any term herein or in any Loan Document and such term is defined differently in different Articles or Divisions of the Code, the definition of such term contained in Article or Division 9 shall govern; provided further, that in the event that, by reason of mandatory provisions of law, any or all of the attachment, perfection, or priority of, or remedies with respect to, Agent's Lien on any Collateral is governed by the Uniform Commercial Code in effect in a jurisdiction other than the Commonwealth of Massachusetts, the term "Code" shall mean the Uniform Commercial Code as enacted and in effect in such other jurisdiction solely for purposes of the provisions thereof relating to such attachment, perfection, priority, or remedies and for purposes of definitions relating to such provisions.

"**Collateral**" is any and all properties, rights and assets of Borrower described on Exhibit A.

"**Collateral Account**" is any Deposit Account, Securities Account, or Commodity Account.

"**Commitment**" and "**Commitments**" means the Term Loan Commitment(s).

"**Commodity Account**" is any "commodity account" as defined in the Code with such additions to such term as may hereafter be made.

"**Compliance Certificate**" is that certain certificate in the form attached hereto as Exhibit B.

"**Contingent Obligation**" is, for any Person, any direct or indirect liability, contingent or not, of that Person for (a) any indebtedness, lease, dividend, letter of credit or other obligation of another such as an obligation, in each case, directly or indirectly guaranteed, endorsed, co-made, discounted or sold with recourse by that Person, or for which that Person is directly or indirectly liable; (b) any obligations for undrawn letters of credit for the account of that Person; and (c) all obligations from any interest rate, currency or commodity swap agreement, interest rate cap or collar agreement, or other agreement or arrangement designated to protect a Person against fluctuation in interest rates, currency exchange rates or commodity prices; but "Contingent Obligation" does not include endorsements in the ordinary course of business. The amount of a Contingent Obligation is the stated or determined amount of the primary obligation for which the Contingent Obligation is made or, if not determinable, the maximum reasonably anticipated liability for it determined by the Person in good faith; but the amount may not exceed the maximum of the obligations under any guarantee or other support arrangement.

"**Control Agreement**" is any control agreement entered into among the depository institution at which Borrower maintains a Deposit Account or the securities intermediary or commodity intermediary at which Borrower maintains a Securities Account or a Commodity Account, Borrower, and Agent pursuant to which Agent obtains control (within the meaning of the Code) for the benefit of the Lenders over such Deposit Account, Securities Account, or Commodity Account.

"**Copyrights**" are any and all copyright rights, copyright applications, copyright registrations and like protections in each work of authorship and derivative work thereof, whether published or unpublished and whether or not the same also constitutes a trade secret.

"**Credit Extension**" is any Term Loan Advance, or any other extension of credit by any Lender for Borrower's benefit.

"**Default Rate**" is defined in Section 2.3(b).

"**Defaulting Lender**" is, subject to Section 10.10(b), any Lender that (a) has failed to (i) fund all or any portion of its Term Loan Advances within two (2) Business Days of the date such Term Loan Advances were required to be funded hereunder unless such Lender notifies Agent and Borrower in writing that such failure is the result of such Lender's reasonable determination that one or more conditions precedent to funding (each of which conditions precedent, together with any applicable default, shall be specifically identified in such writing) has not been satisfied, or (ii) pay to Agent or any other Lender any other amount required to be paid by it hereunder within two (2) Business Days of the date when due, (b) has notified Borrower or Agent in writing that it does not intend to comply with its

funding obligations hereunder, or has made a public statement to that effect (unless such writing or public statement relates to such Lender's obligation to fund a Term Loan Advance hereunder and states that such position is based on such Lender's reasonable determination that a condition precedent to funding (which condition precedent, together with any applicable default, shall be specifically identified in such writing or public statement) cannot be satisfied), (c) has failed, within three (3) Business Days after written request by Agent or Borrower, to confirm in writing to Agent and Borrower that it will comply with its prospective funding obligations hereunder (provided that such Lender shall cease to be a Defaulting Lender pursuant to this clause (c) upon receipt of such written confirmation by Agent and Borrower), or (d) has, or has a direct or indirect parent company that has, (i) become the subject of an Insolvency Proceeding, or (ii) had appointed for it a receiver, custodian, conservator, trustee, administrator, assignee for the benefit of creditors or similar Person charged with reorganization or liquidation of its business or assets, including the Federal Deposit Insurance Corporation or any other state or federal regulatory authority acting in such a capacity; provided that a Lender shall not be a Defaulting Lender solely by virtue of the ownership or acquisition of any equity interest in that Lender or any direct or indirect parent company thereof by a Governmental Authority so long as such ownership interest does not result in or provide such Lender with immunity from the jurisdiction of courts within the United States or from the enforcement of judgments or writs of attachment on its assets or permit such Lender (or such Governmental Authority) to reject, repudiate, disavow or disaffirm any contracts or agreements made with such Lender. Any determination by Agent that a Lender is a Defaulting Lender under any one or more of clauses (a) through (d) above shall be conclusive and binding absent manifest error, and such Lender shall be deemed to be a Defaulting Lender (subject to Section 10.10(b)) upon delivery of written notice of such determination to Borrower and each Lender.

"**Deposit Account**" is any "**deposit account**" as defined in the Code with such additions to such term as may hereafter be made.

"**Designated Deposit Account**" is the account number ending 844 (last three digits) maintained by Borrower with SVB (provided, however, if no such account number is included, then the Designated Deposit Account shall be any deposit account of Borrower maintained with SVB as chosen by the Lenders).

"**Disbursement Letter**" is that certain form attached hereto as Exhibit D.

"**Dollars**," "**dollars**" or use of the sign "$" means only lawful money of the United States and not any other currency, regardless of whether that currency uses the "$" sign to denote its currency or may be readily converted into lawful money of the United States.

"**Dollar Equivalent**" is, at any time, (a) with respect to any amount denominated in Dollars, such amount, and (b) with respect to any amount denominated in a Foreign Currency, the equivalent amount therefor in Dollars as determined by Agent at such time on the basis of the then-prevailing rate of exchange in San Francisco, California, for sales of the Foreign Currency for transfer to the country issuing such Foreign Currency.

"**Draw Period**" is the period of time commencing upon the occurrence of the Milestone Event and continuing through August 15, 2019.

"**Effective Date**" is defined in the preamble hereof.

"**Equipment**" is all "**equipment**" as defined in the Code with such additions to such term as may hereafter be made, and includes without limitation all machinery, fixtures, goods, vehicles (including motor vehicles and trailers), and any interest in any of the foregoing.

"**ERISA**" is the Employee Retirement Income Security Act of 1974, and its regulations.

"**Event of Default**" is defined in Section 8.

"**Exchange Act**" is the Securities Exchange Act of 1934, as amended.

"**Existing Loan Agreement**" is that certain Loan and Security Agreement by and between Borrower and SVB, dated as of November 9, 2016, as amended by that certain First Amendment to Loan and Security Agreement by and between Borrower and SVB, dated as of November 26, 2018.

"**Experimental Compounds**" means biopharmaceutical compounds and therapeutic materials that remain subject to clinical trials and have not yet received regulatory approval.

"**FDA**" shall mean the United States Food and Drug Administration, and any successor thereto.

"**Federal Funds Effective Rate**" means, for any day, the weighted average of the rates on overnight federal funds transactions with members of the Federal Reserve System arranged by federal funds brokers, as published on the next succeeding Business Day by the Federal Reserve Bank of New York, or, if such rate is not so published for any day that is a Business Day, the average of the quotations for the day of such transactions received by SVB from three federal funds brokers of recognized standing selected by it.

"**Final Payment**" is a payment (in addition to and not in substitution for the regular monthly payments of principal plus accrued interest) equal to the original aggregate principal amount of each Term Loan Advance extended by the Lenders to Borrower hereunder multiplied by six percent (6.0%) due on the earliest to occur of (a) the Term Loan Maturity Date, (b) the acceleration of the Term Loan Advances, (c) the prepayment of the Term Loan Advances pursuant to Section 2.2(d) or 2.2(e), or (d) the termination of this Agreement.

"**Foreign Currency**" means lawful money of a country other than the United States.

"**Funding Date**" is any date on which a Credit Extension is made to or for the account of Borrower which shall be a Business Day.

"**FX Contract**" is any foreign exchange contract by and between Borrower and SVB under which Borrower commits to purchase from or sell to SVB a specific amount of Foreign Currency on a specified date.

"**GAAP**" is generally accepted accounting principles set forth in the opinions and pronouncements of the Accounting Principles Board of the American Institute of Certified Public Accountants and statements and pronouncements of the Financial Accounting Standards Board or in such other statements by such other Person as may be approved by a significant segment of the accounting profession, which are applicable to the circumstances as of the date of determination.

"**General Intangibles**" is all "general intangibles" as defined in the Code in effect on the date hereof with such additions to such term as may hereafter be made, and includes without limitation, all Intellectual Property, claims, income and other tax refunds, security and other deposits, payment intangibles, contract rights, options to purchase or sell real or personal property, rights in all litigation presently or hereafter pending (whether in contract, tort or otherwise), insurance policies (including without limitation key man, property damage, and business interruption insurance), payments of insurance and rights to payment of any kind.

"**Governmental Approval**" is any consent, authorization, approval, order, license, franchise, permit, certificate, accreditation, registration, filing or notice, of, issued by, from or to, or other act by or in respect of, any Governmental Authority.

"**Governmental Authority**" is any nation or government, any state or other political subdivision thereof, any agency, authority, instrumentality, regulatory body, court, central bank or other entity exercising executive, legislative, judicial, taxing, regulatory or administrative functions of or pertaining to government, any securities exchange and any self-regulatory organization.

"**Indebtedness**" is (a) indebtedness for borrowed money or the deferred price of property or services, such as reimbursement and other obligations for surety bonds and letters of credit, (b) obligations evidenced by notes, bonds, debentures or similar instruments, (c) capital lease obligations, and (d) Contingent Obligations.

"**Indemnified Person**" is defined in Section 13.3.

"**Insolvency Proceeding**" is any proceeding by or against any Person under the United States Bankruptcy Code, or any other bankruptcy or insolvency law, including assignments for the benefit of creditors, compositions, extensions generally with its creditors, or proceedings seeking reorganization, arrangement, or other relief.

"**Intellectual Property**" means, with respect to any Person, all of such Person's right, title, and interest in and to the following:

(a) any and all Copyrights, Trademarks and Patents;

(b) any and all trade secrets and trade secret rights, including, without limitation, any rights to unpatented inventions, know-how and operating manuals;

(c) any and all source code;

(d) any and all design rights which may be available to such Person;

(e) any and all claims for damages by way of past, present and future infringement of any of the foregoing, with the right, but not the obligation, to sue for and collect such damages for said use or infringement of the Intellectual Property rights identified above; and

(f) all amendments, renewals and extensions of any of the Copyrights, Trademarks or Patents.

"**Inventory**" is all "**inventory**" as defined in the Code in effect on the date hereof with such additions to such term as may hereafter be made, and includes without limitation all merchandise, raw materials, parts, supplies, packing and shipping materials, work in process and finished products, including without limitation such inventory as is temporarily out of Borrower's custody or possession or in transit and including any returned goods and any documents of title representing any of the above.

"**Investment**" is any beneficial ownership interest in any Person (including stock, partnership interest or other securities), and any loan, advance or capital contribution to any Person.

"**Irish Subsidiary**" is a wholly owned Subsidiary of Borrower to be formed in the future under the laws of Ireland.

"**Key Person**" is Borrower's Chief Executive Officer, who is Herriot Tabuteau as of the Effective Date.

"**Lender**" and "**Lenders**" is defined in the preamble.

"**Lender Entities**" is defined in Section 13.9.

"**Lender Intercreditor Agreement**" is, collectively, any and all intercreditor agreement, master arrangement agreement or similar agreement by and between WestRiver and SVB, as each may be amended from time to time in accordance with the provisions thereof.

"**Lenders' Expenses**" are all of Agent's and the Lenders' audit fees and expenses, costs, and expenses (including reasonable attorneys' fees and expenses) for preparing, amending, negotiating, administering, defending and enforcing the Loan Documents (including, without limitation, those incurred in connection with appeals or Insolvency Proceedings) or otherwise incurred with respect to Borrower.

"**Letter of Credit**" is a standby or commercial letter of credit issued by SVB upon request of Borrower based upon an application, guarantee, indemnity, or similar agreement.

"**Lien**" is a claim, mortgage, deed of trust, levy, charge, pledge, security interest or other encumbrance of any kind, whether voluntarily incurred or arising by operation of law or otherwise against any property.

"**Loan Documents**" are, collectively, this Agreement and any schedules, exhibits, certificates, notices, and any other documents related to this Agreement, the Perfection Certificate, the Lender Intercreditor Agreement, each Disbursement Letter, the Warrant, any Bank Services Agreement, any Control Agreement, any subordination agreement, any note, or notes or guaranties executed by Borrower, and any other present or future agreement by Borrower with or for the benefit of Agent and the Lenders in connection with this Agreement or Bank Services, all as amended, restated, or otherwise modified.

"**Material Adverse Change**" is (a) a material impairment in the perfection or priority of Agent's, for the ratable benefit of the Lenders, Lien in the Collateral or in the value of such Collateral; (b) a material adverse change in the business, operations, or condition (financial or otherwise) of Borrower; or (c) a material impairment of the prospect of repayment of any portion of the Obligations.

"**Milestone Event**" means Borrower has provided Agent and the Lenders with evidence, on or prior to August 15, 2019, satisfactory to Agent in Agent's and each Lender's sole but reasonable discretion that Borrower (i) has received positive data with respect to Borrower's phase 2 clinical trial for AXS-12, sufficient to submit a phase 3 protocol to the FDA and (ii) has not received any objections from the FDA within thirty (30) days after submission of such phase 3 protocol.

"**Monthly Financial Statements**" is defined in Section 6.2(a).

"**Obligations**" are Borrower's obligations to pay when due any debts, principal, interest, fees, Lenders' Expenses, the Final Payment, the Prepayment Premium and other amounts Borrower owes Agent or any Lender now or later, whether under this Agreement, the other Loan Documents (other than the Warrant, or otherwise, including, without limitation, all obligations relating to Bank Services, if any, and including any interest accruing after Insolvency Proceedings begin and debts, liabilities, or obligations of Borrower assigned to Agent and/or the Lenders, and to perform Borrower's duties under the Loan Documents (other than the Warrant).

"**Operating Documents**" are, for any Person, such Person's formation documents, as certified by the Secretary of State (or equivalent agency) of such Person's jurisdiction of organization on a date that is no earlier than thirty (30) days prior to the Effective Date, and, (a) if such Person is a corporation, its bylaws in current form, (b) if such Person is a limited liability company, its limited liability company agreement (or similar agreement), and (c) if such Person is a partnership, its partnership agreement (or similar agreement), each of the foregoing with all current amendments or modifications thereto.

"**Patents**" means all patents, patent applications and like protections including without limitation improvements, divisions, continuations, renewals, reissues, extensions and continuations-in-part of the same.

"**Payment/Advance Form**" is that certain form attached hereto as Exhibit C.

"**Payment Date**" is the first (1st) calendar day of each month.

"**Perfection Certificate**" is defined in Section 5.1.

"**Permitted Indebtedness**" is:

(a) Borrower's Indebtedness to Agent and the Lenders under this Agreement and the other Loan Documents;

(b) Indebtedness existing on the Effective Date which is shown on the Perfection Certificate;

(c) Subordinated Debt;

(d) unsecured Indebtedness to trade creditors incurred in the ordinary course of business;

(e) Indebtedness incurred as a result of endorsing negotiable instruments received in the ordinary course of business;

(f) intercompany Indebtedness of the Australian Subsidiary to Borrower with respect to Investments permitted under clause (h) of the definition of Permitted Investments;

(g) Indebtedness secured by Liens permitted under clauses (a) and (c) of the definition of "Permitted Liens" hereunder;

(h) other unsecured Indebtedness not otherwise permitted hereunder, in an aggregate amount not to exceed Twenty-Five Thousand Dollars ($25,000.00) at any time outstanding; and

(i) extensions, refinancings, modifications, amendments and restatements of any items of Permitted Indebtedness (a) through (h) above, provided that the principal amount thereof is not increased or the terms thereof are not modified to impose more burdensome terms upon Borrower or its Subsidiary, as the case may be.

"**Permitted Investments**" are:

(a) Investments (including, without limitation, Subsidiaries) existing on the Effective Date which are shown on the Perfection Certificate;

(c) Investments consisting of (i) Cash Equivalents and (ii) any other Investments permitted by Borrower's Investment Policy and Guidelines dated as of August 2016 and provided to Agent on November 5, 2016, as amended from time to time, provided that any amendments thereto have been approved in writing by Agent and the Lenders;

(d) Investments consisting of deposit and securities accounts to the extent that (i) such accounts are permitted to be maintained pursuant to Section 6.6 and (ii) Agent has a first priority perfected security interest to the extent required under Section 6.6;

(e) Investments accepted in connection with Transfers permitted by Section 7.1;

(f) Investments consisting of (i) travel advances and employee relocation loans and other employee loans and advances in the ordinary course of business, and (ii) loans to employees, officers or directors relating to the purchase of equity securities of Borrower or its Subsidiaries pursuant to employee stock purchase plans or agreements approved by Borrower's Board;

(g) Investments (including debt obligations) received in connection with the bankruptcy or reorganization of customers or suppliers and in settlement of delinquent obligations of, and other disputes with, customers or suppliers arising in the ordinary course of business;

(h) Investments consisting of notes receivable of, or prepaid royalties and other credit extensions, to customers and suppliers who are not Affiliates, in the ordinary course of business; provided that this paragraph (g) shall not apply to Investments of Borrower in any Subsidiary;

(i) Investments (i) by Borrower in Australian Subsidiary for ordinary, necessary and current operating expenses not to exceed One Million Five Hundred Thousand Dollars ($1,500,000.00) in the aggregate in any fiscal year and (ii) by Borrower in Irish Subsidiary for ordinary, necessary and current operating expenses not to exceed Fifty Thousand Dollars ($50,000.00) in the aggregate in any fiscal year, provided, in each case, no Event of Default has occurred and is continuing at the time of such Investments or would result from such Investments; and

(j) non-cash Investments in joint ventures or strategic alliances in the ordinary course of Borrower's business consisting of the non-exclusive licensing of technology, the development of Intellectual Property or the providing of technical support.

"**Permitted Liens**" are:

(a) Liens existing on the Effective Date which are shown on the Perfection Certificate or arising under this Agreement and the other Loan Documents;

(k) Liens for taxes, fees, assessments or other government charges or levies, either (i) not due and payable or (ii) being contested in good faith and for which Borrower maintains adequate reserves on its Books, provided that no notice of any such Lien has been filed or recorded under the Internal Revenue Code of 1986, as amended, and the Treasury Regulations adopted thereunder;

(l) purchase money Liens or capital leases (i) on Equipment acquired or held by Borrower incurred for financing the acquisition of the Equipment securing no more than Fifty Thousand Dollars ($50,000.00) in the aggregate amount outstanding, or (ii) existing on Equipment when acquired, if the Lien is confined to the property and improvements and the proceeds of the Equipment;

(m) Liens of carriers, warehousemen, suppliers, or other Persons that are possessory in nature arising in the ordinary course of business so long as such Liens attach only to Inventory, and which are not delinquent or remain payable without penalty or which are being contested in good faith and by appropriate proceedings which proceedings have the effect of preventing the forfeiture or sale of the property subject thereto;

(n) Liens to secure payment of workers' compensation, employment insurance, old-age pensions, social security and other like obligations incurred in the ordinary course of business (other than Liens imposed by ERISA);

(o) Liens, deposits and pledges to secure the performance of bids, tenders, contracts (other than contracts for the payment of money), public or statutory obligations, surety, stay, appeal, indemnity, performance or other similar bonds or other similar obligations arising in the ordinary course of Borrower's business;

(p) leases or subleases of real property granted in the ordinary course of Borrower's business (or, if referring to another Person, in the ordinary course of such Person's business), and leases, subleases, non-exclusive licenses or sublicenses of personal property (other than Intellectual Property) granted in the ordinary course of Borrower's business (or, if referring to another Person, in the ordinary course of such Person's business), if the leases, subleases, licenses and sublicenses do not prohibit granting Agent a security interest therein;

(q) non-exclusive license of Intellectual Property granted to third parties in the ordinary course of business, and licenses of Intellectual Property that could not result in a legal transfer of title of the licensed property that may be exclusive in respects other than territory and that may be exclusive as to territory only as to discreet geographical areas outside of the United States;

(r) Liens in favor of other financial institutions arising in connection with Borrower's deposit and/or securities accounts held at such institutions (but only to the extent such accounts are permitted to be maintained pursuant to Section 6.6), provided that Agent has a first priority perfected security interest in the amounts held in such deposit and/or securities accounts to the extent required under Section 6.6;

(s) Liens arising from attachments or judgments, orders, or decrees in circumstances not constituting an Event of Default under Sections 8.4 and 8.7; and

(t) Liens incurred in the extension, renewal or refinancing of the indebtedness secured by Liens described in (a) through (c), but any extension, renewal or replacement Lien must be limited to the property encumbered by the existing Lien and the principal amount of the indebtedness may not increase.

"**Person**" is any individual, sole proprietorship, partnership, limited liability company, joint venture, company, trust, unincorporated organization, association, corporation, institution, public benefit corporation, firm, joint stock company, estate, entity or government agency.

"**Prepayment Premium**" shall be an additional fee, payable to Agent, for the ratable benefit of the Lenders based on their Pro Rata Share, with respect to the Term Loan Advances, in an amount equal to:

(a) for a prepayment of the Term Loan Advances made on or prior to the first (1st) anniversary of the Effective Date, three percent (3.0%) of the then outstanding principal amount of the Term Loan Advances immediately prior to the date of such prepayment;

(a) for a prepayment of the Term Loan Advances made after the first (1st) anniversary of the Effective Date, but on or prior to the second (2nd) anniversary of the Effective Date, two percent (2.0%) of the then outstanding principal amount of the Term Loan Advances immediately prior to the date of such prepayment; and

(a) for a prepayment of the Term Loan Advances made after the second (2nd) anniversary of the Effective Date, but prior to the Term Loan Maturity Date, one percent (1.0%) of the then outstanding principal amount of the Term Loan Advances immediately prior to the date of such prepayment.

"**Prime Rate**" is the rate of interest per annum from time to time published in the money rates section of The Wall Street Journal or any successor publication thereto as the "prime rate" then in effect; provided that, in the event such rate of interest is less than zero, such rate shall be deemed to be zero for purposes of this Agreement; and provided further that if such rate of interest, as set forth from time to time in the money rates section of The Wall Street Journal, becomes unavailable for any reason as determined by Agent, the "Prime Rate" shall mean the rate of interest per annum announced by SVB as its prime rate in effect at its principal office in the State of California (such SVB announced Prime Rate not being intended to be the lowest rate of interest charged by SVB in connection with extensions of credit to debtors); provided that, in the event such rate of interest is less than zero, such rate shall be deemed to be zero for purposes of this Agreement.

"**Pro Rata Share**" is, as of any date of determination, with respect to each Lender, a percentage (expressed as a decimal, rounded to the ninth decimal place) determined by *dividing* the outstanding principal amount of Term Loan Advances held by such Lender *by* the aggregate outstanding principal amount of all Term Loan Advances.

"**Registered Organization**" is any "registered organization" as defined in the Code with such additions to such term as may hereafter be made.

"**Repayment Schedule**" means the period of time equal to thirty-six (36) consecutive months; provided, however, if the Term B Loan Advance is made, the Repayment Schedule shall mean the period of time equal to thirty (30) consecutive months.

"**Requirement of Law**" is as to any Person, the organizational or governing documents of such Person, and any law (statutory or common), treaty, rule or regulation or determination of an arbitrator or a court or other Governmental Authority, in each case applicable to or binding upon such Person or any of its property or to which such Person or any of its property is subject.

"**Responsible Officer**" is any of the Chief Executive Officer, President, Chief Financial Officer, VP-Finance, and Controller of Borrower.

"**Restricted License**" is any material license or other material agreement with respect to which Borrower is the licensee (a) that prohibits or otherwise restricts Borrower from granting a security interest in Borrower's interest in such license or agreement or any other property, or (b) for which a default under or termination of could reasonably be expected to interfere with the Agent's right to sell any Collateral.

"**SEC**" shall mean the Securities and Exchange Commission, any successor thereto, and any analogous Governmental Authority.

"**Securities Account**" is any "**securities account**" as defined in the Code with such additions to such term as may hereafter be made.

"**Subordinated Debt**" is indebtedness incurred by Borrower subordinated to all of Borrower's now or hereafter indebtedness to Agent and the Lenders (pursuant to a subordination, intercreditor, or other similar agreement in form and substance satisfactory to Agent and the Lenders entered into between Agent, the Lenders and the other creditor), on terms acceptable to Agent and the Lenders.

"**Subsidiary**" is, as to any Person, a corporation, partnership, limited liability company or other entity of which shares of stock or other ownership interests having ordinary voting power (other than stock or such other ownership interests having such power only by reason of the happening of a contingency) to elect a majority of the

board of directors or other managers of such corporation, partnership or other entity are at the time owned, or the management of which is otherwise controlled, directly or indirectly through one or more intermediaries, or both, by such Person. Unless the context otherwise requires, each reference to a Subsidiary herein shall be a reference to a Subsidiary of Borrower.

"**SVB**" is defined in the preamble hereof.

"**SVB Obligations**" is defined in Section 2.2(a).

"**Term A Loan Advance**" is defined in Section 2.2(a).

"**Term B Loan Advance**" is defined in Section 2.2(a).

"**Term Loan Advance**" and "**Term Loan Advances**" are each defined in Section 2.2(a).

"**Term Loan Amortization Date**" is March 1, 2020; provided, however, if the Term B Loan Advance is made, the Term Loan Amortization Date shall be September 1, 2020.

"**Term Loan Commitment**" means, for any Lender, the obligation of such Lender to make a Term Loan Advance as and when available, up to the principal amount shown on Schedule 1. "Term Loan Commitments" means the aggregate amount of such commitments of all Lenders.

"**Term Loan Commitment Percentage**" means, as to any Lender at any time, the percentage (carried out to the fourth decimal place) of the Term Loan Commitments represented by such Lender's Term Loan Commitment at such time. The initial Term Loan Commitment Percentage of each Lender is set forth opposite the name of such Lender on Schedule 1.

"**Term Loan Maturity Date**" is February 1, 2023.

"**Trademarks**" means any trademark and servicemark rights, whether registered or not, applications to register and registrations of the same and like protections, and the entire goodwill of the business of Borrower connected with and symbolized by such trademarks.

"**Transfer**" is defined in Section 7.1.

"**Warrant**" means, collectively, (a) that certain warrant to purchase stock dated as of the Effective Date between Borrower and SVB and (b) that certain warrant to purchase stock dated as of the Effective Date between Borrower and WestRiver, in each case, as may be amended, modified, supplemented and/or restated from time to time.

"**WestRiver**" is defined in the preamble hereof.

[Signature Page Follows.]

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed as a sealed instrument under the laws of the Commonwealth of Massachusetts as of the Effective Date.

BORROWER:

AXSOME THERAPEUTICS, INC.

By: /s/ Herriot Tabuteau

Name: Herriot Tabuteau

Title: Chief Executive Officer

AGENT:

SILICON VALLEY BANK, as Agent

By: /s/ Lauren Cole

Name: Lauren Cole

Title: Director

LENDERS:

SILICON VALLEY BANK

By: /s/ Lauren Cole

Name: Lauren Cole

Title: Director

WESTRIVER INNOVATION LENDING FUND VIII, L.P.

By: /s/ Trent Dawson

Name: Trent Dawson

Title: Chief Financial Officer

SCHEDULE 1

LENDERS AND COMMITMENTS

TERM LOAN COMMITMENTS

Lender	**Term Loan Commitment**	**Term Loan Commitment Percentage**
Silicon Valley Bank	$12,000,000.00	50.0%
WestRiver Innovation Lending Fund VIII, L.P.	$12,000,000.00	50.0%
TOTAL	**$24,000,000.00**	**100.0000%**

EXHIBIT A - COLLATERAL DESCRIPTION

The Collateral consists of all of Borrower's right, title and interest in and to the following personal property:

All goods, Accounts (including health-care receivables), Equipment, Inventory, contract rights or rights to payment of money, leases, license agreements, franchise agreements, General Intangibles (except as provided below), commercial tort claims, documents, instruments (including any promissory notes), chattel paper (whether tangible or electronic), cash, deposit accounts, certificates of deposit, fixtures, letters of credit rights (whether or not the letter of credit is evidenced by a writing), securities, and all other investment property, supporting obligations, and financial assets, whether now owned or hereafter acquired, wherever located; and

all of Borrower's Books relating to the foregoing, and any and all claims, rights and interests in any of the above and all substitutions for, additions, attachments, accessories, accessions and improvements to and replacements, products, proceeds and insurance proceeds of any or all of the foregoing.

Notwithstanding the foregoing, the Collateral does not include (i) more than sixty-five percent (65.0%) of the presently existing and hereafter arising issued and outstanding shares of capital stock owned by Borrower of Australian Subsidiary and Irish Subsidiary which shares entitle the holder thereof to vote for directors or any other matter, (ii) rights held under a license that are not assignable by their terms without the consent of the licensor thereof (but only to the extent such restriction on assignment is enforceable under applicable law), or (iii) any Intellectual Property; provided, however, the Collateral shall include all Accounts and all proceeds of Intellectual Property. If a judicial authority (including a U.S. Bankruptcy Court) would hold that a security interest in the underlying Intellectual Property is necessary to have a security interest in such Accounts and such property that are proceeds of Intellectual Property, then the Collateral shall automatically, and effective as of the Effective Date, include the Intellectual Property to the extent necessary to permit perfection of Agent's, for the ratable benefit of the Lenders, security interest in such Accounts and such other property of Borrower that are proceeds of the Intellectual Property.

Pursuant to the terms of a certain negative pledge arrangement with Agent and the Lenders, Borrower has agreed not to encumber any of its Intellectual Property in violation of this Agreement without Agent's and the Lenders' prior written consent.

EXHIBIT B
COMPLIANCE Certificate

TO: SILICON VALLEY BANK, as Agent, SVB, and WESTRIVER Date:
FROM: AXSOME THERAPEUTICS, INC.

The undersigned authorized officer of AXSOME THERAPEUTICS, INC. ("**Borrower**") certifies that under the terms and conditions of the Loan and Security Agreement among Borrower, SVB, and WestRiver (the "**Loan Agreement**"):

(1) Borrower is in complete compliance for the period ending _____ with all required covenants except as noted below, (2) there are no Events of Default, (3) all representations and warranties in the Agreement are true and correct in all material respects on this date except as noted below; provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof; and provided, further that those representations and warranties expressly referring to a specific date shall be true, accurate and complete in all material respects as of such date, (4) Borrower, and each of its Subsidiaries, has timely filed all required tax returns and reports (or appropriate extensions therefor), and Borrower has timely paid all foreign, federal, state and local taxes, assessments, deposits and contributions owed by Borrower except as otherwise permitted pursuant to the terms of Section 5.8 of the Agreement, and (5) no Liens have been levied or claims made against Borrower or any of its Subsidiaries relating to unpaid employee payroll or benefits of which Borrower has not previously provided written notification to Agent.

Attached are the required documents supporting the certification. The undersigned certifies that these are prepared in accordance with GAAP consistently applied from one period to the next except as explained in an accompanying letter or footnotes. The undersigned acknowledges that no borrowings may be requested at any time or date of determination that Borrower is not in compliance with any of the terms of the Agreement, and that compliance is determined not just at the date this certificate is delivered. Capitalized terms used but not otherwise defined herein shall have the meanings given them in the Agreement.

Please indicate compliance status by circling Yes/No under "Complies" column.

Reporting Covenants	**Required**	**Complies**
Monthly financial statements with Compliance Certificate	Monthly within 40 days	Yes No
Annual financial statement (CPA Audited)	FYE within 180 days	Yes No
Filed 10-Q, 10-K and 8-K	Within 5 days after filing with SEC	Yes No
10-Q Report, 10-K Report, and annual financial statement	Within 45 days of quarter end for 10-Q; FYE within 90 days for 10-K; and FYE within 90 days for annual financial statements	Yes No
Board-Approved Projections	FYE within 60 days and promptly following changes	Yes No

Other Matters

Have there been any amendments of or other changes to the capitalization table of Borrower and to the Operating Documents of Borrower or any of its Subsidiaries? If yes, provide copies of any such amendments or changes with this Compliance Certificate.	Yes	No

The following are the exceptions with respect to the certification above: (If no exceptions exist, state "No exceptions to note.")

AXSOME THERAPEUTICS, INC.

By:
Name:
Title:

AGENT USE ONLY

Received by: _____
authorized signer
Date: _____

Verified: _____
authorized signer
Date: _____

Compliance Status: Yes No

EXHIBIT C

LOAN PAYMENT/ADVANCE REQUEST FORM

Deadline for same day processing is Noon Eastern Time

Fax To: Date: _____

Loan Payment: AXSOME THERAPEUTICS, INC.

From Account #_____ To Account #_____
(Deposit Account #) (Loan Account #)
Principal $_____ and/or Interest $_____

Authorized Signature: Phone Number:
Print Name/Title:

Loan Advance:

Complete *Outgoing Wire Request* section below if all or a portion of the funds from this loan advance are for an outgoing wire.

From Account #_____ To Account #_____
(Loan Account #) (Deposit Account #)

Amount of Term Loan Advance $_____

All Borrower's representations and warranties in the Loan and Security Agreement are true, correct and complete in all material respects on the date of the request for an advance; provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof; and provided, further that those representations and warranties expressly referring to a specific date shall be true, accurate and complete in all material respects as of such date:

Authorized Signature: Phone Number:
Print Name/Title:

Outgoing Wire Request:
Complete only if all or a portion of funds from the loan advance above is to be wired.
Deadline for same day processing is noon, Eastern Time

Beneficiary Name: _____ Amount of Wire: $
Beneficiary Bank: _____ Account Number:
City and State:

Beneficiary Bank Transit (ABA) #: Beneficiary Bank Code (Swift, Sort, Chip, etc.):
(For International Wire Only)
Intermediary Bank: Transit (ABA) #:
For Further Credit to:

Special Instruction:

By signing below, I (we) acknowledge and agree that my (our) funds transfer request shall be processed in accordance with and subject to the terms and conditions set forth in the agreements(s) covering funds transfer service(s), which agreements(s) were previously received and executed by me (us).

Authorized Signature: _____ 2nd Signature (if required): _____
Print Name/Title: _____ Print Name/Title: _____
Telephone #: Telephone #:

Exhibit D

Form of Disbursement Letter

[see attached]

DISBURSEMENT LETTER

[DATE]

The undersigned, being the duly elected and acting of **AXSOME THERAPEUTICS, INC.**, a Delaware corporation ("**Borrower**"), does hereby certify, in their capacity as an officer of Borrower and not individually, to (a) **SILICON VALLEY BANK**, a California corporation ("**SVB**"), in its capacity as administrative agent and collateral agent ("**Agent**"), (b) **SILICON VALLEY BANK**, a California corporation, as a lender, (c) **WESTRIVER INNOVATION LENDING FUND VIII, L.P.**, a Delaware limited partnership ("**WestRiver**"), as a lender (SVB and WestRiver and each of the other "Lenders" from time to time a party hereto are referred to herein collectively as the "**Lenders**" and each individually as a "**Lender**") in connection with that certain Loan and Security Agreement dated as of March 5, 2019, by and among Borrower, Agent and the Lenders from time to time party thereto (the "**Loan Agreement**"; with other capitalized terms used below having the meanings ascribed thereto in the Loan Agreement) that:

1. The representations and warranties made by Borrower in Section 5 of the Loan Agreement and in the other Loan Documents are true and correct in all material respects as of the date hereof.

2. No event or condition has occurred that would constitute an Event of Default under the Loan Agreement or any other Loan Document.

3. Borrower is in compliance with the covenants and requirements contained in Sections 4, 6 and 7 of the Loan Agreement.

4. All conditions referred to in Section 3 of the Loan Agreement to the making of a Credit Extension to be made on or about the date hereof have been satisfied or waived by Agent.

5. No Material Adverse Change has occurred.

6. The undersigned is an Authorized Signer.

[Balance of Page Intentionally Left Blank]

7. The proceeds of the Term Loan Advance shall be disbursed as follows:

Disbursement from SVB:	
Loan Amount	$_____
Plus:	
--Deposit Received	$_____
Less:	
--Payoff of Silicon Valley Bank	($_____)
--Lender's Legal Fees	($_____)*
Net Proceeds due from SVB:	**$_____**
Disbursement from WestRiver:	
Loan Amount	$_____
Plus:	
--Deposit Received	$_____
Net Proceeds due from WestRiver:	**$_____**
TOTAL TERM LOAN ADVANCE NET PROCEEDS FROM LENDERS	**$_____**

8. The aggregate net proceeds of the Term Loan Advance shall be transferred to the Designated Deposit Account as follows:

Account Name:	_____
Bank Name:	Silicon Valley Bank
Bank Address:	3003 Tasman Drive Santa Clara, California 95054
Account Number:	_____
ABA Number:	_____

[Balance of Page Intentionally Left Blank]

Dated as of the date first set forth above.

BORROWER:

AXSOME THERAPEUTICS, INC.

By
Name:
Title:

AGENT AND LENDER:

SILICON VALLEY BANK

By
Name:
Title:

LENDER:
SILICON VALLEY BANK

By
Name:
Title:

LENDER:

WESTRIVER INNOVATION LENDING FUND
VIII, L.P.

By
Name:
Title:

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statements:

- Registration Statement (Form S-8 No. 333-217002) pertaining to the Axsome Therapeutics, Inc. 2015 Omnibus Incentive Compensation Plan,
- Registration Statement (Form S-8 No. 333-208579) pertaining to the Axsome Therapeutics, Inc. 2015 Omnibus Incentive Compensation Plan
- Registration Statement (Form S-8 No. 333-226824) pertaining to Axsome Therapeutics, Inc. 2015 Omnibus Incentive Compensation Plan, and
- Registration Statement (Form S-3 No. 333-214859) of Axsome Therapeutics, Inc. and in the related Prospectus;

of our report dated March 14, 2019, with respect to the consolidated financial statements of Axsome Therapeutics, Inc. included in this Annual Report (Form 10-K) of Axsome Therapeutics, Inc. for the year ended December 31, 2018.

/s/ Ernst & Young LLP

New York, NY
March 14, 2019

Exhibit 31.1

CERTIFICATION OF PERIODIC REPORT
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Herriot Tabuteau, certify that:

1. I have reviewed this annual report on Form 10-K of Axsome 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 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 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: March 14, 2019

/s/ Herriot Tabuteau
Herriot Tabuteau
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF PERIODIC REPORT PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Nick Pizzie, certify that:

1. I have reviewed this annual report on Form 10-K of Axsome 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 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 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: March 14, 2019

/s/ Nick Pizzie
Nick Pizzie
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

STATEMENT OF PRINCIPAL EXECUTIVE OFFICER OF
AXSOME THERAPEUTICS, INC.
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of Axsome Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2018 as filed with the Securities and Exchange Commission (the "Report"), I, Herriot Tabuteau, M.D., Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. §1350, as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that, based on my knowledge:

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

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

Date: March 14, 2019

/s/ Herriot Tabuteau, M.D.
Herriot Tabuteau, M.D.
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

STATEMENT OF PRINCIPAL FINANCIAL OFFICER OF
AXSOME THERAPEUTICS, INC.
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of Axsome Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2018 as filed with the Securities and Exchange Commission (the "Report"), I, Nick Pizzie, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. §1350, as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that, based on my knowledge:

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

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

Date: March 14, 2019

/s/ Nick Pizzie
Nick Pizzie
Chief Financial Officer
(Principal Financial and Accounting Officer)