

**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, 2019

OR

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

For the transition period from \_\_\_\_\_ to \_\_\_\_\_

Commission File Number 001-37635

**AXSOME THERAPEUTICS, INC.**

(Exact name of registrant as specified in its charter)

**Delaware**

(State or other jurisdiction of  
incorporation or organization)

**45-4241907**

(I.R.S. Employer  
Identification No.)

**200 Broadway**

**3<sup>rd</sup> Floor**

**New York, New York**

(Address of principal executive offices)

**10038**

(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  
(Title of Class)

Nasdaq Global Market  
(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 pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes  No

Indicate by check mark 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 filer, 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).

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 \$675.0 million as of June 28, 2019, based on the closing sale price of such stock as reported on the Nasdaq Global Market.

There were 37,075,422 shares of the registrant's common stock outstanding as of March 6, 2020.

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's definitive proxy statement for its 2020 Annual Meeting of Stockholders (the "Proxy Statement"), to be filed within 120 days of the registrant's fiscal year ended December 31, 2019, 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, 2019**

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## 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 five CNS product candidates, AXS-05, AXS-07, AXS-09, AXS-12, and AXS-14 which are being developed for multiple indications. AXS-05 is currently in a Phase 3 trial in treatment resistant depression, or TRD, which we refer to as the STRIDE-1 study, a Phase 3 open-label safety trial in patients with TRD and major depressive disorder, or MDD, and a Phase 2/3 trial in agitation associated with Alzheimer's disease, or AD, which we refer to as the ADVANCE-1 study. For AXS-05, we have completed a Phase 2 trial and Phase 3 trial in MDD, which we refer to as the ASCEND study and the GEMINI study, respectively. We plan to file a New Drug Application, or NDA, for AXS-05 for the treatment of MDD based on the ASCEND and GEMINI trials. AXS-05 is also being developed for smoking cessation and a Phase 2 trial in the indication has been completed. AXS-07 is currently in a Phase 3 trial for the acute treatment of migraine, which we refer to as the INTERCEPT study and a Phase 3 open-label safety trial in patients with migraine. For AXS-07, we have completed a Phase 3 trial for the acute treatment of migraine, which we refer to as the MOMENTUM study. We plan to file an NDA for AXS-07 for the acute treatment of migraine based on the MOMENTUM trial. AXS-09 is being developed for the treatment of CNS disorders. AXS-12 is being developed for the treatment of narcolepsy. We have completed a Phase 2 trial with AXS-12, which we refer to as the CONCERT study. AXS-14 is being developed for the treatment of fibromyalgia. Additionally, we are currently evaluating other product candidates, which we intend to develop for CNS disorders. The Axsome Pain and Primary Care business unit, or Axsome PPC, houses our pain and primary care assets. 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 a proprietary formulation and dose of bupropion and dextromethorphan, or DM, and utilizes our metabolic inhibition technology. We are developing AXS-05 initially for the following four indications: MDD, TRD, agitation associated with AD, 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, rapidly absorbed, multi-mechanistic, investigational medicine. AXS-07 consists of MoSEIC™, or Molecular Solubility Enhanced Inclusion Complex, meloxicam and rizatriptan. We are developing AXS-07 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<sub>max</sub>, 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<sub>1B/D</sub> 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 NMDA receptor antagonist with multimodal activity 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. AXS-12 has been granted Orphan Drug Designation by the FDA for the treatment of narcolepsy.

AXS-14, esreboxetine, is a novel, oral, investigational medicine in development for the treatment of fibromyalgia. AXS-14 is a highly selective and potent norepinephrine reuptake inhibitor. We are initially developing esreboxetine for the treatment of fibromyalgia. Esreboxetine, the SS-enantiomer of reboxetine, is more potent and selective than racemic reboxetine.

The Axsome Pain and Primary Care business unit, or Axsome PPC, houses our pain and primary care assets, and includes intellectual property which covers these and related product candidates and molecules being developed by us and others.

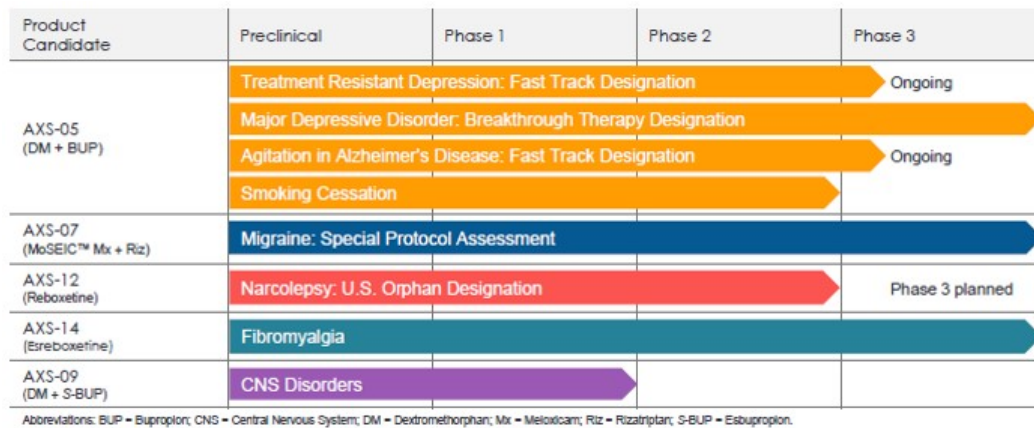
Our product candidates are protected through a combination of patents, trade secrets, and proprietary know-how. If approved, they may also be eligible for periods of regulatory exclusivity. Our intellectual property portfolio includes issued U.S. and foreign patents with claims extending to 2034 for AXS-05 and to 2036 for AXS-07, as well as U.S. and foreign patent applications for AXS-05, AXS-07, AXS-09, AXS-12, and AXS-14.

## 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 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-07 product candidate. 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.
- **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:



**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 a proprietary formulation and dose 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 multiple mechanisms of action. We are developing AXS-05 initially as a therapeutic for major depressive disorder, or MDD, treatment resistant depression, or TRD, agitation associated with Alzheimer’s disease, or AD, 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 seasonal affective disorder, or SAD, 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 7.1% of U.S. adults, or approximately 17.3 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 7.1% of U.S. adults experience MDD each year, and of them 64% had severe impairment associated with their depression. 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.* AXS-05 is an NMDA receptor antagonist with multimodal activity. DM's mechanisms of action encompass those of several currently marketed antidepressant drugs such as esketamine (Spravato), duloxetine (Cymbalta), fluoxetine (Prozac), and fluvoxamine (Luvox). Bupropion inhibits the reuptake of dopamine and is a nicotinic acetylcholine 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.



## **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 (Aricept), and behavioral disorders, such as fluvoxamine, include sigma-1 receptor agonism. Furthermore, the mechanism of NMDA antagonism is a treatment for dementia, such as with memantine (Namenda).

### **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. Both bupropion and DM are nicotine receptor antagonists.

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.

In April 2019 we announced the positive results of a Phase 2 trial for smoking cessation with AXS-05 that was conducted at Duke University. The results showed that AXS-05 met the prespecified primary endpoint and significantly reduced daily smoking as compared to the active comparator bupropion.

***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 one Phase 2 trial and one Phase 3 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.

In March 2019, we received FDA Breakthrough Therapy designation for AXS-05 for the treatment of MDD.

In April 2019, we announced that AXS-05 met the prespecified primary endpoint in Phase 2 trial in smoking cessation.

In May 2019, we announced pivotal status of the ASCEND trial allowing for expedited development of AXS-05 for the treatment of MDD based on the outcome of an FDA Breakthrough Therapy meeting.

In June 2019, we initiated the GEMINI study, a Phase 3, randomized, double-blind, multicenter, placebo-controlled trial of AXS-05 in the treatment of MDD.

In July 2019, we announced that we initiated an open-label study in order to build a patient safety database to support the filing of an NDA for AXS-05 for the treatment of MDD.

In December 2019, we announced that AXS-05 achieved the primary endpoint and rapidly and significantly improved symptoms of depression in the GEMINI study.

#### *Completed GEMINI Study*

We have completed the GEMINI Phase 3 study, a randomized, double-blind, placebo-controlled, multi-center, U.S. trial, in which 327 adult patients with confirmed moderate to severe MDD were randomized to treatment with either AXS-05 (45 mg dextromethorphan/ 105 mg bupropion modulated delivery tablet) or placebo once daily for the first 3 days and twice daily thereafter for a total of 6 weeks.

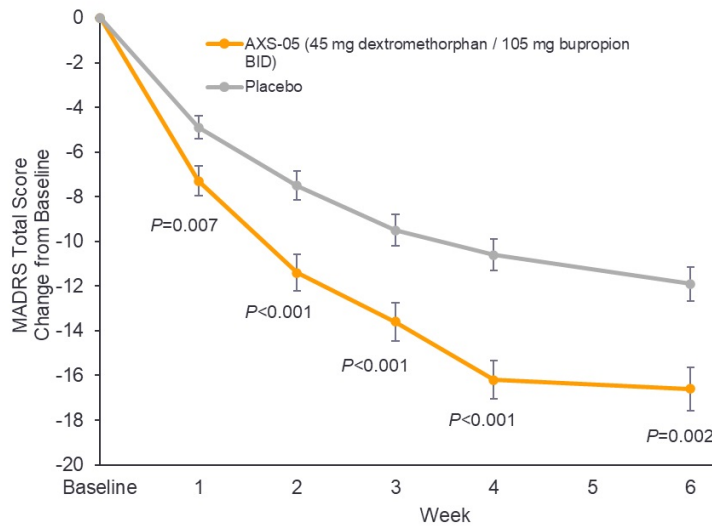
AXS-05 met the primary endpoint by demonstrating a highly statistically significant reduction in the Montgomery-Åsberg Depression Rating Scale, or MADRS, total score compared to placebo at Week 6, with mean reductions from baseline of 16.6 points for AXS-05 and 11.9 points for placebo ( $p=0.002$ ). AXS-05 rapidly and durably improved depressive symptoms as compared to placebo with statistical significance on the MADRS total score demonstrated at Week 1, the earliest time point assessed, and at all time points thereafter. Rates of remission from depression (defined as MADRS  $\leq 10$ ) were statistically significantly greater for AXS-05 compared to placebo at Week 2 ( $p=0.013$ ) and at every time point thereafter, being achieved by 39.5% of AXS-05 patients compared to 17.3% of placebo patients at Week 6 ( $p<0.001$ ).

AXS-05 demonstrated rapid onset of action with statistically significant improvement as compared to placebo on numerous endpoints at Week 1, or only 4 days after receiving the target dose of AXS-05. Statistically significant improvements at Week 1 were observed for MADRS total score (key secondary endpoint,  $p=0.007$ ); Patient Global Impression-Improvement, or PGI-I, ( $p=0.008$ ); Clinical Global Impression-Severity, or CGI-S, ( $p=0.013$ ); Clinical Global Impression-Improvement, or CGI-I, ( $p=0.035$ ); Quick Inventory of Depressive Symptomatology-Self-Rated, or QIDS-SR-16, ( $p=0.016$ ); Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, or Q-LES-Q-SF, ( $p=0.031$ ); and other endpoints.

On all secondary endpoints including the following, AXS-05 demonstrated statistically significant improvement at Week 6 compared to placebo, reflecting increasing treatment effects over time: clinical response on the MADRS total score (defined as  $\geq 50\%$ ) ( $p < 0.001$ ); PGI-I ( $p = 0.007$ ); CGI-S ( $p = 0.002$ ); CGI-I ( $p = 0.016$ ); QIDS-SR-16 ( $p = 0.001$ ); Sheehan Disability Scale (SDS) ( $p = 0.002$ ); and Q-LES-Q-SF ( $p = 0.011$ ).

AXS-05 was well tolerated in the trial. The most commonly reported adverse events in the AXS-05 arm were dizziness, nausea, headache, diarrhea, somnolence, and dry mouth. There was one serious adverse event in the AXS-05 arm which was deemed by the investigator not to be study-drug related. The rates of discontinuation due to adverse events were low in both treatment groups (6.2% for AXS-05 and 0.6% for placebo). Treatment with AXS-05 was not associated with psychotomimetic effects or weight gain.

**Depressive symptom change with AXS-05 in patients with MDD in the GEMINI Phase 3 trial**



	AXS-05 (n=156)	Placebo (n=162)	Difference	P-Value
<b>Primary Endpoint</b>				
Change in MADRS Total Score at Week 6	-16.6	-11.9	-4.7	0.002
<b>Key Secondary Endpoint</b>				
Change in MADRS Total Score at Week 1	-7.3	-4.9	-2.4	0.007

Notes: P-values calculated from LSMean. Abbreviations: BID = twice daily; MADRS = Montgomery-Åsberg Depression Rating Scale

**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 modulated delivery tablet), or the active comparator bupropion (105 mg), twice daily for 6 weeks.

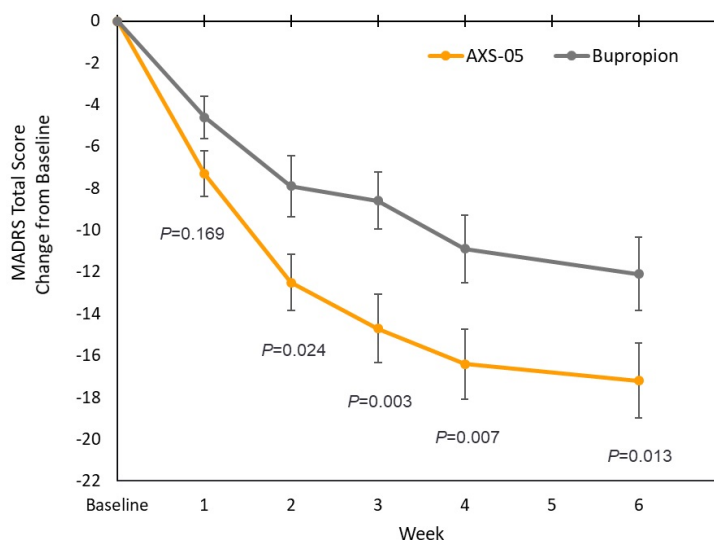
AXS-05 met the prespecified primary endpoint by demonstrating a highly statistically significant reduction in the MADRS total score, averaged over the 6-week treatment period, the overall treatment effect, as compared to bupropion ( $p < 0.001$ ). At Week 6, AXS-05 demonstrated a 17.2 point reduction 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 CGI-I at Week 1 ( $p = 0.045$ ). Starting at Week 1, or only four days after receiving the target dose, 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  $\geq 50\%$  reduction from baseline, ( $p = 0.014$  at Week 6); CGI-I ( $p = 0.045$  at Week 1, and 0.051 at Week 6); CGI-S ( $p = 0.038$  at Week 6); percentage of patients achieving remission on MADRS, remission defined as MADRS  $\leq 10$ , ( $p = 0.004$  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.

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



	AXS-05	Bupropion	P-Value
<b>Primary Endpoint</b>			
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

*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.

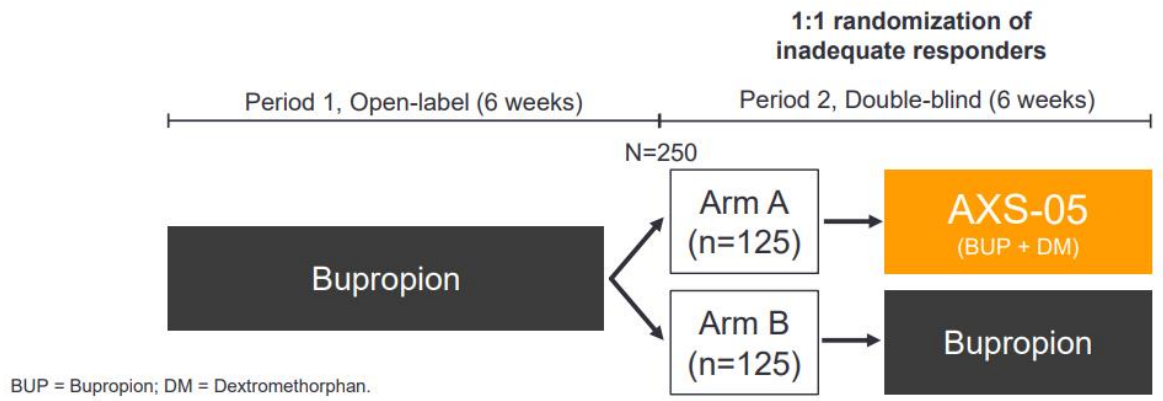
There were no reported serious adverse events in the trial. The majority of treatment-emergent adverse events experienced were graded as mild or moderate in severity, and had resolved by the end of the study. The most commonly reported adverse events were dizziness, nausea, headache, insomnia, dry mouth, 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.

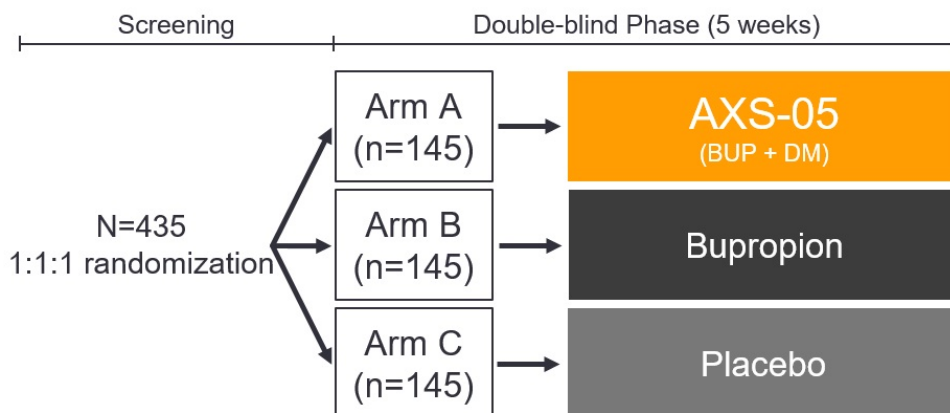
The third Phase 1 trial was a randomized, multiple-dose, double-blind pharmacokinetic study of AXS-05 conducted using a single tablet containing DM and bupropion. In this study, which enrolled a total of 30 healthy, adult volunteers, administration of AXS-05 as a single tablet resulted in substantial 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.

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.





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 in 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.



BUP = Bupropion; DM = Dextromethorphan.

## AXS-07

### Overview

AXS-07 is novel, oral, rapidly absorbed, multi-mechanistic, investigational medicine. AXS-07 consists of MoSEIC™ meloxicam and rizatriptan. We are 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, photophobia, 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 clinical evidence of improvements in migraine pain and most bothersome symptom as well as the mechanisms of action of both components of AXS-07. 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.

*Mechanistic rationale.* 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. In addition, MoSEIC™ meloxicam 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. The rizatriptan component of AXS-07 is a 5-HT<sub>1B/D</sub> 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.

#### *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.

In May 2019, we announced the acceleration of the timeline for reporting topline results from the MOMENTUM study.

In July 2019, we announced that we are enrolling an open-label study in order to build safety databases of patients to support the filing of a New Drug Application, or NDA for AXS-07 in the acute treatment of migraine.

In September 2019, we announced positive results from a Phase 1 pharmacokinetic trial of AXS-07.

In October 2019, we initiated the INTERCEPT study, a Phase 3, randomized, double-blind, multicenter, placebo-controlled trial evaluating the early treatment of migraine with AXS-07.

In October 2019, we announced the results of the MINDSET physician survey, which affirms the unmet need and favorable profile of AXS-07 in the acute treatment of migraine.

In December 2019, we announced that AXS-07 achieved co-primary and key secondary endpoints and significantly improved migraine pain, freedom from most bother symptom, and sustained pain freedom, in the MOMENTUM study.

#### *Completed MOMENTUM Study*

MOMENTUM was a randomized, double-blind, placebo- and active-controlled trial which enrolled only patients with a history of inadequate response to prior acute migraine treatments, assessed using the Migraine Treatment Optimization Questionnaire, or mTOQ-4. A total of 1,594 patients were randomized in a 2:2:2:1 ratio to AXS-07 (20 mg MoSEIC™ meloxicam/10 mg rizatriptan), rizatriptan (10 mg), MoSEIC™ meloxicam (20 mg), or placebo, to treat a single migraine attack of moderate or severe intensity. In addition to a history of inadequate response, enrolled patients exhibited a high rate of characteristics that are strongly associated with poor treatment outcomes including cutaneous allodynia (75.4%), severe migraine pain intensity (41.2%), obesity (43.7%), and morning migraine (36.6%). The study was conducted pursuant to an FDA Special Protocol Assessment, or SPA. Rizatriptan, an active comparator in the trial, is considered to be the fastest acting oral triptan and one of the most effective medications currently available for the acute treatment of migraine.

AXS-07 met the two regulatory co-primary endpoints by demonstrating, with high statistical significance, a greater percentage of patients as compared to placebo achieving pain freedom (19.9% versus 6.7%,  $p < 0.001$ ) and absence of most bothersome symptom (36.9% versus 24.4%,  $p = 0.002$ ), 2 hours after dosing. Superiority of AXS-07 to rizatriptan and MoSEIC™ meloxicam (component contribution) was established as specified in the SPA, by demonstration of a greater percentage of AXS-07 patients achieving sustained pain freedom from 2 to 24 hours after dosing, compared to rizatriptan and MoSEIC™ meloxicam, as well as to placebo (16.1%, 11.2%, 8.8% and 5.3%, respectively;  $p = 0.038$ ,  $p = 0.001$ , and  $p < 0.001$ , respectively versus AXS-07).

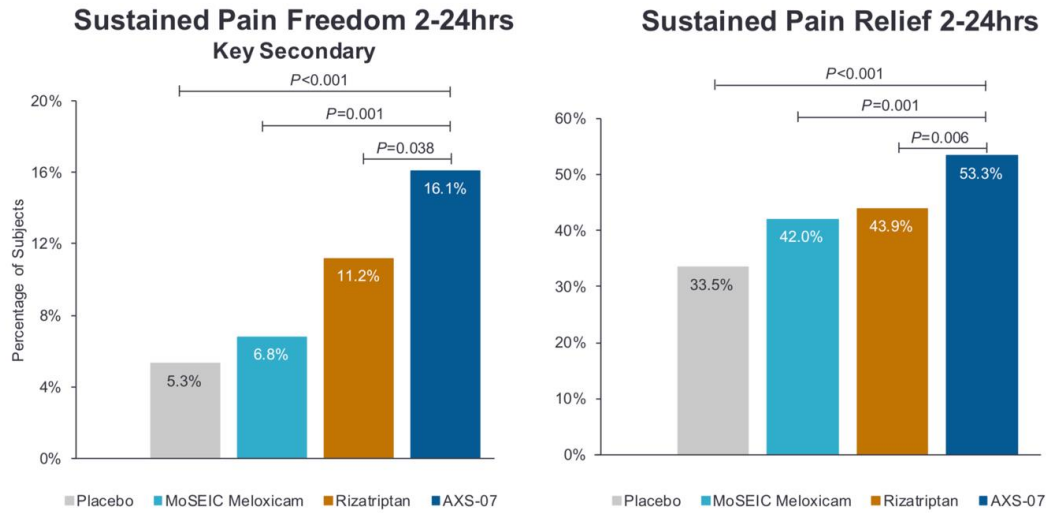
AXS-07 provided substantially greater and more sustained migraine pain relief compared to placebo and rizatriptan, which translated to a significant reduction in rescue medication use for AXS-07 compared to placebo and rizatriptan. The percentage of patients experiencing sustained pain relief from 2 to 24 hours after dosing was 53.3% for AXS-07, compared to 33.5% for placebo and 43.9% for rizatriptan ( $p < 0.001$ ,  $p = 0.006$ , respectively versus AXS-07). Sustained pain relief from 2 to 48 hours was also experienced by a statistically significantly greater proportion of AXS-07 patients (46.5%), compared to placebo (31.1%) and rizatriptan (36.5%) patients ( $p < 0.001$ ,  $p = 0.003$ , respectively versus AXS-07). Rescue medication was used by 23.0% of AXS-07 patients, compared to 43.5% of placebo and 34.7% of rizatriptan patients ( $p < 0.001$  for each group versus AXS-07).

AXS-07 provided rapid relief of migraine pain with the percentage of patients achieving pain relief with AXS-07 being numerically greater than with rizatriptan at every time point measured starting at 15 minutes, and statistically significantly greater than with rizatriptan by 60 minutes ( $p = 0.04$ ). The proportions of patients experiencing pain relief 1.5 hours after dosing were 60.5% for AXS-07 compared to 52.5% for rizatriptan and 48.3% for placebo ( $p = 0.019$ ,  $p = 0.004$ , respectively versus AXS-07). AXS-07 was statistically significantly superior to rizatriptan on several other secondary endpoints including PGI-C ( $p = 0.022$ ), and return to normal functioning at 24 hours ( $p = 0.027$ ).

AXS-07 was safe and well tolerated in the trial. The most commonly reported adverse events with AXS-07 were nausea, dizziness and somnolence, none of which occurred at a rate greater than placebo or greater than 3%. There was one serious adverse event in the AXS-07 arm which was deemed by the investigator not to be related to study drug.

The MOMENTUM study was conducted pursuant to an SPA with the FDA. The SPA provides agreement that the overall MOMENTUM trial design (e.g., entry criteria, dose selection, endpoints) and planned analysis adequately address objectives that, if met, will support filing of an NDA of AXS-07 for the indication of acute treatment of migraine in adults with or without aura.

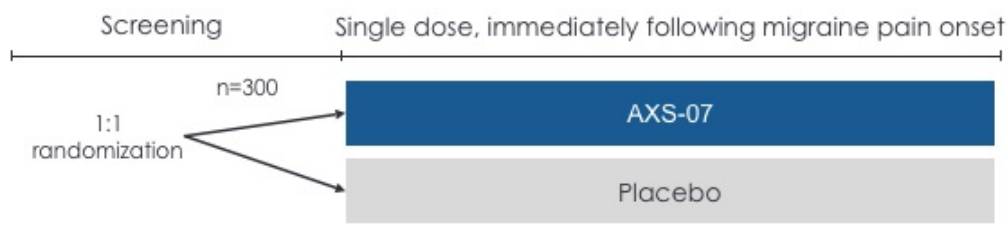
**Results of AXS-07 MOMENTUM Phase 3 Trial for the treatment of acute migraine**



Co-Primary Endpoints	AXS-07 (n=428)	Placebo (n=209)	Difference	P-Value
Endpoint 1: Pain Freedom 2 Hours after Dose, %	19.9%	6.7%	-13.2%	<0.001
Endpoint 2: Absence of Most Bothersome Symptom 2 Hours after Dose, %	36.9%	24.4%	-12.5%	0.002

*Ongoing INTERCEPT Study*

In October 2019, we initiated the INTERCEPT study, a Phase 3, randomized, double-blind, placebo-controlled trial evaluating the early treatment of migraine with AXS-07. Patients are randomly assigned in a 1:1 ratio to receive AXS-07 or placebo in a double-blind fashion. Patients are to administer AXS-07 at the earliest sign of migraine pain. 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, or phonophobia) two hours after dosing. The trial will randomize a total of approximately 300 patients.



## **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.

#### ***Rationale for the Development of AXS-12 in Narcolepsy***

The rationale for the development of AXS-12 in narcolepsy is supported by positive pre-clinical and clinical results in narcolepsy, and an extensive clinical safety record. 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.

*Mechanistic rationale.* Animal models have demonstrated that adrenergic neurotransmission play an important role in cataplexy. Compounds acting on noradrenergic transmission strongly suppressed canine cataplexy at low doses. In contrast, serotonergic uptake blockers were only partially active against cataplexy at high doses, and dopaminergic agents were inactive. AXS-12 is a potent norepinephrine reuptake inhibitor. In a murine model of narcolepsy, reboxetine dose-dependently reduced the number of narcoleptic episodes in orexin-deficient mice ( $p < 0.0001$ ). Reboxetine also significantly reduced the total duration of time spent in narcoleptic episodes ( $p < 0.0001$ ). A comparison with the serotonin reuptake inhibitor escitalopram in this same model revealed a median effective dose (ED50) for reboxetine (0.012 mg/kg) that was markedly lower than for escitalopram (0.44 mg/kg), suggesting that selective inhibition of norepinephrine reuptake may be more potent in treating cataplexy than selective inhibition of serotonin reuptake. Currently approved pharmacological treatments for cataplexy and excessive daytime sleepiness, or, EDS have mechanisms which include inhibition of norepinephrine reuptake.

### ***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.

In December 2019, we announced that AXS-12 met the prespecified primary endpoint and significantly reduced the total number of cataplexy attacks in the CONCERT Phase 2 trial.

In January 2020, we entered into an exclusive license agreement with Pfizer Inc. for Pfizer's clinical and nonclinical data, and intellectual property for reboxetine, the active pharmaceutical ingredient in AXS-12.

#### *Completed CONCERT Study*

CONCERT was a Phase 2, randomized, double-blind, placebo-controlled, crossover, multicenter, U.S. trial in which 21 patients with a diagnosis of narcolepsy with cataplexy were all treated with orally administered AXS-12 for 2 weeks, and with placebo for 2 weeks, with the treatment periods separated by 1 week of down-titration and washout.

AXS-12 met the prespecified primary endpoint by demonstrating a highly statistically significant reduction from baseline in the mean weekly number of cataplexy attacks, averaged for the 2-week treatment period, the overall treatment effect, as compared to placebo ( $p < 0.001$ ). At Week 2, AXS-12 demonstrated a mean reduction of 14.6 cataplexy attacks per week compared to a reduction of 2.6 attacks per week for placebo ( $p = 0.002$ ), representing mean reductions of 48.8% and 8.6% from baseline, respectively. The proportion of patients achieving a 50% or greater reduction in the weekly number of cataplexy attacks was 76.2% for AXS-12, compared to 30.0% for placebo ( $p = 0.003$ ) at Week 2. The improvement in cataplexy was rapid with AXS-12 demonstrating significant benefit over placebo as early as Week 1 ( $p < 0.001$ ).

AXS-12 significantly improved EDS symptoms compared to placebo, as measured by the Epworth Sleepiness Scale, or ESS, and by the frequency of inadvertent naps. The improvement on the ESS with AXS-12 treatment was twice that observed with placebo, with reductions from baseline in the ESS score of 6.0 and 3.1, respectively for AXS-12 and placebo ( $p = 0.003$ ). AXS-12 treatment resulted in a 31.8% mean reduction from baseline in the average weekly number of inadvertent naps versus a 5.3% mean reduction for placebo ( $p < 0.001$ ) at Week 2. The improvement in frequency of inadvertent naps was rapid with AXS-12 demonstrating significant benefit over placebo as early as Week 1 ( $p = 0.038$ ).

AXS-12 significantly improved cognitive function compared to placebo over the 2-week treatment period as measured by the Ability to Concentrate item of the Narcolepsy Symptom Assessment Questionnaire (NSAQ), which was assessed daily ( $p < 0.001$ ). For this assessment, patients rated their ability to concentrate on a 5-point scale (1=very good to 5=very poor). At the end of treatment, 42.9% of patients had an ability to concentrate that was “good” to “very good” with AXS-12 treatment, compared to 25.0% of patients with placebo, and 0% of patients at baseline. The improvement in the ability to concentrate was rapid with AXS-12 demonstrating significant improvement over placebo as early as Week 1 ( $p = 0.007$ ).

AXS-12 significantly improved sleep quality, as measured by overall improvement and by number of awakenings at night, and reduced sleep-related symptoms, as compared to placebo. AXS-12 treatment resulted in 45.0% of patients reporting improved sleep quality versus 5.3% of patients with placebo ( $p = 0.007$ ). AXS-12 treatment resulted in 30.0% of patients reporting a reduction in the number of awakenings at night versus 5.3% of patients with placebo ( $p = 0.044$ ). AXS-12 treatment also resulted in greater proportions of patients with reductions in sleep paralysis episodes, and in hypnagogic hallucinations, as compared to placebo ( $p = ns$ ).

AXS-12 was safe and well tolerated. There were no serious adverse events reported in the trial, and no discontinuations due to adverse events. The overall percentage of patients experiencing adverse events was 42.9% with AXS-12 and 40.0% with placebo, with the most commonly reported adverse events with AXS-12 treatment being anxiety, constipation, and insomnia. The completion rate was 91% for patients randomized to treatment sequence 1 (AXS-12 followed by placebo) and 100% for those randomized to sequence 2 (placebo followed by AXS-12).

## **AXS-14**

### **Overview**

AXS-14, esreboxetine, is a highly selective and potent norepinephrine reuptake inhibitor for the treatment of fibromyalgia and other conditions. Esreboxetine, the SS-enantiomer of reboxetine, is more potent and selective than racemic reboxetine.

### **Fibromyalgia**

#### *Indication Overview*

Fibromyalgia is a chronic disorder often characterized by widespread pain, fatigue, disturbed sleep, depression, and cognitive impairment. Other symptoms of this disorder can include tingling in the hands and feet and headaches. Fibromyalgia is considered to be mediated mainly in the central nervous system. Approximately 5 million Americans, 90% of whom are women, are estimated to suffer from fibromyalgia. Treatment options for fibromyalgia are limited with only three pharmacologic treatments currently approved by the FDA.

#### *Rationale for the Development of AXS-14 in Fibromyalgia*

The rationale for the development of AXS-14 in the treatment of fibromyalgia is based on the mechanism of action of esreboxetine in fibromyalgia and is supported by clinical efficacy and safety results.

*Mechanistic rationale.* Esreboxetine is the S,S-enantiomer of racemic reboxetine, the S,S-enantiomer is more potent and selective than racemic reboxetine. In the spinal cord, inhibition of norepinephrine reuptake enhances descending norepinephrine transmission to the spinal cord, which produces analgesic effects. Thus, selective norepinephrine reuptake inhibition by esreboxetine is expected to provide effective pain relief for the treatment of chronic pain. Current pharmacological treatments for fibromyalgia have mechanisms which include norepinephrine reuptake inhibition, such as duloxetine (Cymbalta) and milnacipran (Savella).

### **Clinical Development of AXS-14**

In January 2020, Axsome received from Pfizer an exclusive license to develop and commercialize esreboxetine in the U.S. for fibromyalgia and all other indications. The license encompasses nonclinical and clinical data for esreboxetine including results from a positive Phase 3 and a positive Phase 2 trial of esreboxetine in the treatment of fibromyalgia conducted by Pfizer.

In a Phase 3 trial conducted by Pfizer in 1,122 patients with fibromyalgia treated with esreboxetine or placebo for 14 weeks, the study met the two primary endpoints demonstrating statistically significant improvements compared to placebo in the weekly mean pain score ( $p < 0.001$ ,  $p < 0.001$ , and  $p = 0.025$ , for 4 mg, 8 mg and 10 mg daily doses, respectively), and the Fibromyalgia Impact Questionnaire, or FIQ, total score ( $p < 0.001$ ,  $p < 0.001$ , and  $p = 0.023$ , for 4 mg, 8 mg and 10 mg doses, respectively). Esreboxetine also resulted in statistically significant improvements as compared to placebo on the PGI-C scale ( $p = 0.002$ ,  $p = 0.001$ , and  $p = 0.007$ , for 4 mg, 8 mg and 10 mg doses, respectively), and in fatigue as measured using the Global Fatigue Index ( $p = 0.001$  and  $p = 0.001$ , for 4 mg and 8 mg daily doses, respectively).

In a Phase 2 trial conducted by Pfizer in 267 patients with fibromyalgia treated with esreboxetine (dose escalated to 8 mg/day) or placebo for 8 weeks, esreboxetine met its primary endpoint demonstrating statistically significant improvements compared to placebo in the weekly mean pain score ( $p = 0.006$ ). The study also demonstrated statistically significant improvements in additional efficacy outcomes including the FIQ total score ( $p < 0.001$ ), the PGIC scale ( $p < 0.001$ ), and fatigue as measured using the Multidimensional Assessment of Fatigue scale ( $p < 0.001$ ).

### **Axsome PPC Product Candidates**

Axsome PPC houses our pain and primary care assets, including AXS-02 and AXS-06, which we are not currently developing. AXS-02 (zoledronic acid) 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. AXS-06 is a novel, oral, investigational medicine consisting of MoSEIC™ meloxicam and esomeprazole.

### **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

### *Exclusive License Agreements with Antecip*

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.

### *Exclusive License Agreement with Pfizer*

In January 2020, we entered into an agreement with Pfizer Inc., or Pfizer for an exclusive U.S. license to Pfizer's clinical and nonclinical data, and intellectual property for reboxetine, the active pharmaceutical ingredient in AXS-12 which Axsome is developing for the treatment of narcolepsy. The agreement also provides Axsome exclusive rights to develop and commercialize esreboxetine, a new late-stage product candidate now referred to as AXS-14, in the U.S. for the treatment of fibromyalgia. Under the terms of the agreement, we received from Pfizer an exclusive U.S. license to Pfizer data for reboxetine and esreboxetine encompassing a full range of nonclinical studies, and short-term and long-term clinical trials involving more than five thousand patients. The licensed data includes results of a positive Phase 3 and a positive Phase 2 trial of esreboxetine in the treatment of fibromyalgia. we will have the exclusive right and sole responsibility of developing AXS-14 (esreboxetine) in the U.S. for the treatment of fibromyalgia and for other indications. Pfizer received 82,019 shares of our common stock having a value of \$8 million, based on the average closing price of our common stock for the 10 prior trading days of \$97.538, in consideration for the license and rights. Pfizer also received an upfront cash payment of \$3 million and will receive up to \$323 million in regulatory and sales milestones, and tiered mid-single to low double-digit royalties on future sales. Pfizer will also have a right of first negotiation on any potential future strategic transactions involving AXS-12 and AXS-14. Under the agreement, we are obligated to use commercially reasonable efforts to develop, manufacture and commercialize the compounds and products in the United States and seeking and maintaining regulatory approvals for the compounds and products. The agreement will expire on a product-by-product basis upon expiration of the last-to-expire royalty term for such product. On expiration (but not earlier termination), we will have a perpetual, non-exclusive, fully paid, royalty-free and irrevocable license under the licensed patent rights and related data to develop, manufacture, use, commercialize and otherwise exploit the compounds. Either party may terminate the agreement for the other party's material breach following a cure period. Pfizer may immediately terminate the agreement upon certain insolvency events relating to us. We may terminate the agreement for any reason upon ninety days written notice to Pfizer at any time after the first anniversary of the agreement.

## 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 6, 2020, 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. Support for this team will include sales management, internal sales support, distribution support, and an internal marketing group. Additional requisite capabilities will include Value and Access inclusive of 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 achieve broader reach or call frequency with other United States target 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 Relmada Therapeutics, Inc., Sage Therapeutics, Inc. and Minerva Neurosciences. 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 deuterated dextromethorphan 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., Treximet, which is marketed by Pernix Therapeutics Holdings, Inc., Reyvow, which is marketed by Eli Lilly and Company Nurtec, which is marketed by Biohaven Pharmaceuticals, and Ubrelvy, which is marketed by Allergan plc.

### ***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, Xyrem and Sunosi, which are both marketed by Jazz Pharmaceuticals plc; and Wakix which is marketed by Harmony Biosciences LLC. We are aware of several companies developing compounds for the treatment of the symptoms of narcolepsy including Avadel Pharmaceuticals plc; and Jazz Pharmaceuticals plc.

### ***AXS-14 Competition***

Products approved to treat fibromyalgia include Cymbalta, which is marketed by Eli Lilly and Company; Lyrica, which is marketed by Pfizer, Inc.; and Savella, which is marketed by Allergan plc. We are aware of other companies working to develop therapeutics for the treatment of fibromyalgia including Astellas Pharma, Inc.; Aptinyx Inc.; Innovative Med Concepts, Inc.; Teva Pharmaceutical Industries Ltd; and Tonix Pharmaceutical Holding Corp.

## **Manufacturing**

Manufacturing of the drug substance and drug product for our drugs and product candidates are done by third-parties and must comply with FDA current good manufacturing practice, or cGMP, regulations. Our product candidates are comprised of 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](http://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, and if approved, program fees must be paid on an annual 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 will determine within 60 days whether the NDA as filed is sufficiently complete to permit a substantive review (with this decision often referred to as the NDA being “accepted 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 goal dates. The review process and the PDUFA goal 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 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 in its current form 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 (from receipt) 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 is an application 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, under state substitution laws, may be substituted at the pharmacy for the reference listed drug.

In seeking approval for a drug through an NDA, including a 505(b)(2) NDA, applicants are required to identify to the FDA patents that contain claims that are directed to the applicant's product and/or method(s) of use. Upon approval of an NDA, each of the identified patents is then listed in *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the Orange Book.

An applicant who files an ANDA seeking approval of a generic 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) in the applicant's opinion and to the best of its knowledge, the patent is invalid, unenforceable, 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 automatic 30-month stay.

In practice, where an ANDA or 505(b)(2) NDA applicant files a paragraph IV certification, the NDA holder or patent owners often take action to trigger the automatic 30-month stay, resulting in patent litigation that may take many months or years to resolve. Thus, approval of an ANDA or 505(b)(2) application 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.

#### *Regulatory Exclusivity*

Regulatory exclusivity provisions under the FDCA can also delay the submission or the approval effective date of certain applications. A regulatory exclusivity can provide the holder of an approved NDA protection from new competition in the marketplace for the innovation represented by its approved drug. Five years of exclusivity are available for 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 NCE exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA application 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.

Three years of exclusivity are 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 drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations, other than bioavailability studies, conducted by the sponsor that were essential to approval of the application. Changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use may be granted this exclusivity if a new clinical investigation (NCI) was essential to approval of the application containing those changes. During the NCI exclusivity period, FDA may not approve an ANDA or 505(b)(2) NDA by another company for the condition of the new drug's approval. NCE and NCI exclusivities will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to, all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy.

Pediatric exclusivity is a regulatory exclusivity in the United States that 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 periods described above as well as applicable patent terms. 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. 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. Orphan drug designation also entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and application user-fee waivers.

#### *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, if an applicant obtains “rolling review” the FDA may accept and initiate review of sections of an NDA before the application submission is complete, although it is not guaranteed that FDA will commence review before the application submission is complete, and the timing of the review depends on a number of factors including availability of review personnel at the FDA, and competing agency priorities among other things. The applicant must provide and the FDA must agree to a schedule for the remaining information after the initial section of the NDA.

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 of receipt, 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; drug supply chain security surveillance and tracking requirements; 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. Further, the FDA has not materially changed its position on off-label promotion following legal setbacks on First Amendment grounds and the DOJ has consistently asserted in FCA briefings that "speech that serves as a conduit for violations of the law is not constitutionally protected."

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 certain 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. Product identifier information (an aspect of the product tracing scheme) is also now required. The DSCSA requirements, development of standards, and the system for product tracing have been and will continue to be phased in over a period of years through 2023, and subject companies will need to continue their implementation efforts. Many states still have in place licensure and other requirements for manufacturers and distributors of drug products. The distribution of product samples continues to be regulated under the PDMA, and some states also impose regulations on drug sample distribution.

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, 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, marketing, distribution, medical education, sponsorships, relationships with prescribers and other referral sources, 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 the Office of Inspector General, or OIG, and the Health Resources and Services Administration, or HRSA, 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, however, 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. The ACA further amended the federal civil False Claims Act to provide that a claim that includes items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim under the False Claims Act. Therefore, either the federal government or private citizens under the False Claims Act’s qui tam provisions (discussed further below) can bring an action under the False Claims Act for violations of the Anti-Kickback Statute, potentially exposing an alleged violator to substantial monetary damages and penalties. Certain Anti-Kickback safe harbor provisions that protect the rebates paid by drug manufacturers to third parties may also be repealed or materially revised, as contemplated in a recent 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 Anti-Kickback 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. Additionally, the federal government has pursued electronic health record (EHR) vendors and pharmaceutical manufacturers for remunerative relationships involving the EHR platform’s recommendation of particular drugs and “prompting” technology to increase prescribing of particular drugs.

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).



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, or overpayments caused by understated rebate amounts. 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 statutes impose 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 for healthcare benefits, items, or services. These statutes are not limited to items and services reimbursed by a governmental health care program and have been used to prosecute commercial insurance fraud as well.

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 statute 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. Further, employment or contracting with an individual or entity that has been excluded from participation in federal healthcare programs could serve as a basis to invalidate claims for items or services submitted by that entity and to exclude that entity from participation in such programs as well. 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 resulting 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 under the 340B Drug Pricing Program, and report the ceiling price to HRSA within Department of Health and Human Services. Manufacturers can be audited by HRSA and be subjected to civil monetary penalties for knowingly and intentionally overcharging covered entities for drugs.

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, extended certain requirements relating to the privacy, security, and transmission of individually identifiable health information directly to business associates of HIPAA-covered entities. A business associate is 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. We are not a covered entity under HIPAA but in certain limited situations, we may be considered a business associate. 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. The FTC's authority under Section 5 is concurrent with HIPAA's jurisdiction and with any action taken under state law.

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, was made effective January 1, 2020. The CCPA, among other things, created new data privacy obligations for covered companies and provided new privacy rights to California residents, including the right to opt out of certain disclosures of their information. The CCPA also created a private right of action with statutory damages for certain data breaches, thereby potentially increasing risks associated with a data breach. 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, and it remains unclear what language the final Attorney General regulations will contain or how the statute and the regulations 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.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under such laws, it is possible that certain business activities could be subject to challenge under one or more of such laws. The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between pharmaceutical companies and providers and patients, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring that business arrangements with third parties comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource-consuming and can divert management's attention from the business, even if investigators ultimately find that no violation has occurred.

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 and potential access restrictions. 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. Governmental and private payors may also establish certain access restrictions, such as prior approvals or evidence of failure on existing medications or therapies. 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.

Pharmacy benefit managers, or PBM, rebates and pricing transparency are key areas of legislative and regulatory focus and there may be changes in the regulatory landscape that could have a significant impact on the pharmaceutical supply chain and drug pricing more generally, which 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 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. There have been numerous initiatives on the federal and state levels in the United States for comprehensive reforms affecting the payment for, the availability of, and reimbursement for, healthcare services. In particular, there have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States. Recent U.S. Congressional inquiries and proposed and enacted federal and state legislation have also been released and are designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. Recent federal budget proposals have included measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. The U.S. Congress and the Trump Administration have indicated that they will continue to seek new legislative and administrative measures to control drug costs, including by addressing the role of PBMs in the supply chain. Current and future U.S. legislative healthcare reforms may result in price controls and other restrictions for any approved products, if covered, and could seriously harm our business. Drug pricing is and will remain a key bipartisan issue in the coming year. If drug pricing reform is not meaningfully addressed before the 2020 election, policies to be pursued in the future may be more aggressive, regardless of which party controls the White House. Given that drug pricing controls is a key legislative and administration priority, it is likely that additional pricing controls will be enacted and could harm our business, financial condition and results of operations. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Some states, such as California, have enacted transparency laws that require manufacturers to report drug price increases and related information. The boom in state laws targeting drug pricing is unprecedented and the requirements are not uniform from state to state, creating additional compliance and commercialization challenges for manufacturers. We further 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.



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, on December 15, 2019, a federal district court in Texas struck down the ACA in its entirety, finding that the Tax Cuts and Jobs Act of 2017 (TCJA) rendered the individual mandate unconstitutional. The judge further concluded in *Texas v. Azar* that since the individual mandate is “essential” to the ACA, it could not be severed from the rest of the ACA and therefore, the entire ACA was unconstitutional. Despite its decision, however, the court did not issue an injunction and therefore, immediate compliance is not required. In addition, the Trump Administration announced that it will continue to administer the law until a formal decision is made by the U.S. Supreme Court. The Supreme Court recently announced that it will hear a challenge in *Texas v. United States*, though arguments have not yet been set. It is likely that the case will be scheduled for arguments early in the next term that starts in October 2020. Apart from *Texas v. United States*, ACA litigation continues across the country in district and appellate courts, and before the Supreme Court. The Supreme Court will issue at least two ACA-related decisions before the end of its current term: one on the risk corridors program (*Maine Community Health Options v. United States*) and the other on religious or moral exemptions to the contraceptive mandate (*Trump v. Pennsylvania* and *Little Sisters of the Poor v. Pennsylvania*). Both decisions are expected before July 2020. It is unclear how the eventual decisions from the Supreme Court and the various other courts across the country to repeal and replace the ACA will impact the ACA and our business. It is also unclear how regulations and sub-regulatory policy, which fluctuate continually, may affect interpretation and implementation of the ACA and its practical effects on our business, particularly entering an election year.

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 \$53.6 million, \$23.5 million, and \$20.0 million for the years ended December 31, 2019, 2018, and 2017, 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-14, AXS-02, and AXS-06.

### **Employees**

As of March 6, 2020, we had 45 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 200 Broadway, 3<sup>rd</sup> Floor, New York, New York 10038, 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 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) the last day of the fiscal year following the fifth anniversary of our initial public offering (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.

As such, we anticipate that we will no longer be an emerging growth company as of December 31, 2020.

## 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 \$68.3 million and \$31.0 million for the years ended December 31, 2019 and 2018, respectively. As of December 31, 2019, we had an accumulated deficit of \$175.9 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 trial with AXS-05 for the treatment of depression;
- conduct our open-label safety extension trial for AXS-05;
- 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 trial with AXS-07 for the acute treatment of migraine;
- conduct our open-label safety extension trial for AXS-07;
- conduct our planned Phase 3 clinical trial 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 may 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 will be sufficient to fund our anticipated operating cash requirements for at least two years. 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., or the 2019 Term Loan, consisting of an initial \$20.0 million tranche, or the Term A Loan Advance, which was funded shortly upon closing, with the remaining \$4.0 million, or the Term B Loan Advance, initially 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, which we refer to as the Milestone Event. 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 to be fully repaid and completed. The new term loan facility matures in February 2023 and initially had an interest-only monthly payment period for twelve months, extendable to eighteen months upon funding of the Term B Loan Advance. We refer to the Term A Loan Advance and the Term B Loan Advance together as the Loan Advances.

In July 2019, we entered into a first amendment to the loan and security agreement, or the First Amendment to the 2019 Term Loan. Under the First Amendment to the 2019 Term Loan, the interest-only monthly payment period of the 2019 Term Loan was extended to 18 months after the date of the 2019 Term Loan, which may be further extended to 24 months upon receipt by us of the Term B Loan Advance. Our ability to draw down the Term B Loan Advance was extended to December 31, 2019, subject to our achievement of the Milestone Event prior to or on December 31, 2019. The Loan Advances mature on February 1, 2023, which we refer to as the Maturity Date.

Pursuant to the 2019 Term Loan, as amended by the First Amendment to the 2019 Term Loan, following the interest-only payment period, we will begin making monthly payments of principal in equal monthly installments for 30 consecutive months (provided, that, upon the occurrence of the Milestone Event, the repayment schedule will be decreased to 24 consecutive months) and monthly payments of 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 First Amendment to the 2019 Term Loan increased the final payment fee, payable upon our repayment of the Loan Advances from 6.0% to 6.30% of the original principal amount of the Loan Advances.

We may prepay all, but not less than all of the Loan Advances, subject to a prepayment fee of 3.0% of any amount prepaid prior to the first anniversary of July 25, 2019, or the First Amendment Effective Date, 2.0% of the amount prepaid if the prepayment occurs after the first anniversary of the First Amendment Effective Date through and including the second anniversary of the First Amendment Effective Date, or 1.0% of the amount prepaid if the prepayment occurs after the second anniversary of the First Amendment Effective Date, but prior to the Maturity Date. These percentages are unchanged from the original 2019 Term Loan.



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 2019 Term Loan if an event of default occurs under the 2019 Term Loan. Under the 2019 Term Loan, an event of default will occur if, among other things, we fail to make payments under the 2019 Term Loan; we breach any of our covenants under the 2019 Term 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. While our current cash reserves are sufficient to repay such indebtedness if an event of default were to occur in the near term, we may in the future 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 2019 Term Loan, subject to the covenants and limitations described in the 2019 Term 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-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, and our second Phase 3 trial with AXS-07 for treatment of acute migraine in October 2019. We began enrolling patients in two open-label safety studies for (i) AXS-05 in the treatment of depression and (ii) AXS-07 in the acute treatment of migraine in July 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 completed 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. The independent data monitoring committee recommended continuation of our COAST-1 trial and discontinuation of our CREATE-1 trial for futility. We had paused screening in the COAST-1 trial prior to the conduct of the interim analysis for that trial and currently, we are in the process of closing out the trial. We conducted one interim analysis for the ongoing Phase 3 trial of AXS-05 in TRD and one interim analysis for the 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, hepatotoxicity, 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, arrhythmia, 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.***

Under the Hatch-Waxman Act, the holder of patents listed in the Orange Book for 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.

In practice, companies that produce branded reference listed drugs often bring patent litigation against applicants that seek regulatory approval to market generic or reformulated versions of their 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 a court finds patents valid and infringed by our product candidates, we may be required to cease selling, relinquish or destroy existing stock, or pay monetary damages 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 have not been finally resolved by the courts, an approach 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, metamorphosis, 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 expedited review for 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 may 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, since providers are not prohibited from prescribing medications for indications other than the approved indications listed on the label. 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.

The FDA may undertake a reevaluation of aspects of its orphan drug regulations and policies at any time, and may possibly do so in response to a recent court decision regarding the plain meaning of the exclusivity provision of the Orphan Drug Act. 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 compliant 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 and may be subject to additional regulatory restrictions associated with the operation of a contracted sales force. 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. Third party payors may also implement onerous access controls, which could further impede our efforts to effectively transition eligible patients to our therapies.

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, monitoring, 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. The FDA must verify our contract manufacturers' compliance with cGMP requirements and comparable foreign regulatory authorities will similarly inspect our contract manufacturers' facilities 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.

***The COVID-19 outbreak and actions taken in response could impact our business.***

In December 2019, a novel strain of coronavirus that causes a respiratory disease named coronavirus disease 2019, or COVID-19, was reported to have surfaced in Wuhan, China. This virus has now spread to numerous other countries, including, as of March 10, 2020, 115 countries and territories around the world and one international conveyance on the Diamond Princess cruise ship.

The extent to which COVID-19 may impact our results will depend on future developments, which are highly uncertain and cannot be predicted, including new information which may emerge concerning the continued spread, transmission, and severity of COVID-19, and actions to treat, contain, or mitigate the impact of COVID-19, including with respect to travel, personnel and workforce, supply chain logistics and import/export, and financial markets or otherwise. We may be impacted indirectly or directly by COVID-19 as among the potentially impacted persons and entities are governmental regulators with oversight responsibilities related to our business, our collaboration partners, clinical study sites, contractors, vendors, and our own personnel and workforce.

For example, we may utilize contract manufacturers to manufacture our investigational products and plan to utilize contract manufacturers if and when we obtain FDA approval. On March 10, 2020, the FDA announced that it is postponing most foreign inspections through April 2020, effective immediately. Inspections outside the U.S. deemed mission-critical will still be considered on a case-by-case basis. This action may impact other FDA responsibilities, including product candidate application reviews. The FDA has indicated that it will utilize interim measures such as reviewing a firm's previous compliance history, using information shared from foreign governments as part of mutual recognition and confidentiality agreements and requesting records "in advance of or in lieu of" on-site drug inspections. Nevertheless, we cannot predict at this time whether this or other developments will cause delays or cause other situations that may impact our business.

***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, which could expose us to significant False Claims Act liability and other civil monetary penalties.

***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.

## 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, was filed at the USPTO by Grunenthal; 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 are some 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, but we later dropped the appeal.

In February 2018, we responded to and opposed the petition for the '268 patent. In May 2018, the PTAB rendered a decision to institute a post-grant review for the patent. In August 2018, we responded to the PTAB decision to institute a post-grant review. In April 2019, the PTAB entered a final written decision holding that the claims were invalid for lack of enablement, but left several of the grounds raised in the Petition unaddressed. In June, we filed a request for rehearing with the PTAB.

In October 2018, the PTAB rendered a decision to institute a post grant review for the '245 patent. In January 2019, we responded to the petition to institute a post-grant review. In October 2019, the PTAB entered a final written decision holding that the claims were invalid for lacking novelty and for obviousness. In November 2019 we filed a request for rehearing with the Precedential Opinion Panel (POP). In February 2020, the POP denied the request, and the request is now under consideration by the original PTAB panel.

In February 2019, the PTAB rendered a decision to institute a post-grant review for the '999 patent. In May 2019, we responded to the petition to institute a post-grant review. In February 2020, the PTAB entered a final written decision holding that thirteen of the claims were valid, and seventeen of the claims were invalid for lacking novelty.

In May 2019, the PTAB rendered a decision to institute a post-grant review for the '839 patent. In October 2019, we responded to the petition to institute a post-grant review.

In July 2019, the PTAB rendered a decision to institute a post-grant review for the '352 patent. In October 2019, we responded to the petition to institute a post-grant review.

In July 2019, the PTAB rendered a decision to institute a post-grant review for the '774 patent. In October 2019, we responded to the petition to institute a post-grant review.

In August 2019, the PTAB rendered a decision to institute a post-grant review for the '338 patent. In October 2019, we responded to the petition to institute a post-grant review.

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 have licensed and may need to license certain intellectual property from third parties in the future, such licenses may not be available or may not be available on commercially reasonable terms, and if the licenses are terminated for any reason our business may be materially harmed.***

We are a party to certain license agreements under which we are granted rights to intellectual property, including patent rights that are important to our business. We expect that we may need to enter into additional license agreements in the future to commercialize our products, in which case we would be required to obtain a license from additional third parties. Such licenses 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 rely on these licenses to use intellectual property that may be material to our business and important or necessary to the development or commercialization of our products. Our existing license agreements impose, and we expect that future license agreements will impose on us, various exclusivity obligations. If we fail to comply with our obligations under these agreements, the applicable licensor may have the right to terminate our license, in which case we may not be able to develop or commercialize the products covered by such license.

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. We are dependent upon the license agreements with Antecip and 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.



In January 2020, we entered into an agreement with Pfizer Inc., or Pfizer, for an exclusive U.S. license to Pfizer's clinical and nonclinical data, and intellectual property for reboxetine, the active pharmaceutical ingredient in AXS-12 which Axsome is developing for the treatment of narcolepsy. The agreement also provides Axsome exclusive rights to develop and commercialize esreboxetine, a new late-stage product candidate now referred to as AXS-14, in the U.S. for the treatment of fibromyalgia. Under the terms of the agreement, we received from Pfizer an exclusive U.S. license to Pfizer data for reboxetine and esreboxetine encompassing a full range of nonclinical studies, and short-term and long-term clinical trials involving more than five thousand patients. The licensed data includes results of a positive Phase 3 and a positive Phase 2 trial of esreboxetine in the treatment of fibromyalgia. We will have the exclusive right and sole responsibility of developing AXS-14 (esreboxetine) in the U.S. for the treatment of fibromyalgia and for other indications. Pfizer received 82,019 shares of our common stock having a value of \$8 million, based on the average closing price of our common stock for the 10 prior trading days of \$97.538, in consideration for the license and rights. Pfizer also received an upfront cash payment of \$3 million and will receive up to \$323 million in regulatory and sales milestones, and tiered mid-single to low double-digit royalties on future sales. Pfizer will also have a right of first negotiation on any potential future strategic transactions involving AXS-12 and AXS-14. Under the agreement, we are obligated to use commercially reasonable efforts to develop, manufacture and commercialize the compounds and products in the United States and seeking and maintaining regulatory approvals for the compounds and products. The agreement will expire on a product-by-product basis upon expiration of the last-to-expire royalty term for such product. On expiration (but not earlier termination), we will have a perpetual, non-exclusive, fully paid, royalty-free and irrevocable license under the licensed patent rights and related data to develop, manufacture, use, commercialize and otherwise exploit the compounds. Either party may terminate the agreement for the other party's material breach following a cure period. Pfizer may immediately terminate the agreement upon certain insolvency events relating to us. We may terminate the agreement for any reason upon ninety days written notice to Pfizer at any time after the first anniversary of the agreement. If the license agreement with Pfizer is terminated for any reason, our business, financial condition, results of operations, and prospects will be materially harmed.

***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 transparency 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 Physician Payments Sunshine 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 laws 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. Many private payors employ "new-to-market blocks" for newly launched medications and other products until the payors have had the opportunity to make a coverage decision based upon their internal review of such products. When a medication or other product is not covered, the patient is responsible to pay the full price, which can significantly limit utilization. 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. Additionally, drug pricing is a key state and federal issue within the U.S., with recent legislation and additional proposals designed to bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare and Medicaid, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. We expect continued focus and pressure on drug pricing going forward, regardless of the results of the 2020 presidential election. 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 or have fewer access restrictions 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, there have been numerous attempts by Congress and the Trump Administration, through legislation and executive orders, to repeal or materially modify various aspects of ACA. In addition, there have been multiple law suits challenging the constitutionality of the ACA as well as various components of the ACA, and it is unclear what impact these various efforts have and will have on our business operations and resulting financial condition. Next term, the Supreme Court will hear arguments on the constitutionality of the ACA, in particular with respect to *Texas v. Azar's* holding that the TCJA rendered the individual mandate unconstitutional and by extension, the entirety of the ACA. It is unclear how the eventual decisions from the Supreme Court and the various other courts across the country to repeal and replace the ACA will impact the ACA and our business. It is also unclear how regulations and sub-regulatory policy, which fluctuate continually, may affect interpretation and implementation of the ACA and its practical effects on our business, particularly entering an election year. We are unable to predict the future course of federal or state healthcare legislation in the United States directed at broadening the availability of healthcare and containing or lowering the cost of healthcare, including drugs and biologics. The fate of the ACA and any further changes in the law or regulatory framework that reduce our revenue or increase our costs could also have a material and adverse effect on our business, financial condition and results of operations.

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 also an increasing focus on the price of drugs, both at the state and federal levels, and it is likely that additional pricing controls will be enacted and could harm our business, financial condition and results of operations. For instance, states such as California have begun enacting transparency laws aimed at curbing drug price increases and both the U.S. Congress and the Trump Administration have indicated that they will continue to seek new legislative and administrative measures to control drug costs. 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 certain 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. Product identifier information (an aspect of the product tracing scheme) is also now required. The DSCSA requirements, development of standards, and the system for product tracing have been and will continue to be phased in over a period of years through 2023, and subject companies will need to continue their implementation efforts. Many states still have in place licensure and other requirements for manufacturers and distributors of drug products. The distribution of product samples continues to be regulated under the PDMA, and some states also impose regulations on drug sample distribution.

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. Further, even if we are successful in mounting a defense, we may incur substantial costs in preparing and maintaining our defense and any such action would be time- and resource-intensive and potentially divert management's attention from the business, which could adversely affect our ability to operate our business and our results of operations.

***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 6, 2020, we had only 45 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. Further, the value to employees of stock options that vest over time is significantly affected by movements in our stock price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies. 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.

***Our continued growth could strain our personnel resources and infrastructure, and if we are unable to implement appropriate controls and procedures to manage our growth, we will not be able to implement our business plan successfully.***

We have experienced a period of recent, rapid growth in our stock price. To the extent that we are able to sustain such growth, it will place a significant strain on our management, administrative, operational and financial infrastructure. Our success will depend in part upon the ability of our senior management to manage this growth effectively. To do so, we must continue to hire, train and manage new employees as needed. If our new hires perform poorly, or if we are unsuccessful in hiring, training, managing and integrating these new employees, or if we are not successful in retaining our existing employees, our business would be harmed. To manage the expected growth of our operations and personnel, we will need to continue to improve our operational, financial and management controls and our reporting systems and procedures.

***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.” As of December 31, 2020, we will no longer be an “emerging growth company”. As such, we will incur significant additional expenses that we did not previously incur in complying with the Sarbanes-Oxley Act and rules implemented by the SEC. The cost of compliance with Section 404 requires us to incur substantial accounting expense and expend significant management time on compliance-related issues as we implement additional corporate governance practices and comply with reporting requirements. Moreover, if we or our independent registered public accounting firm identifies deficiencies in our internal control over financial reporting as material weaknesses, we may be required to make prospective or retroactive changes to our financial statements, consider other areas for further attention or improvement, or be unable to obtain the required attestation in a timely manner, if at all. In addition, the market price of our stock could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources.

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.

In addition, the Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting. In particular, Section 404 of the Sarbanes-Oxley Act will require us to perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on, and our independent registered public accounting firm to attest to, the effectiveness of our internal control over financial reporting. Pursuant to Section 404, as of December 31, 2020, once we are no longer an “emerging growth company,” we will be required to provide an annual management report on the effectiveness of our internal control over financial reporting and we will also be required to include with such annual report an attestation report on internal controls over financial reporting issued by our independent registered public accounting firm. At such time, our independent registered public accounting firm may issue a report that is adverse in the event that we have not maintained effective internal controls over financial reporting, in all material respects. Any failure to maintain effective disclosure controls and internal control over financial reporting could have a material and adverse effect on our business, results of operations and financial condition and could cause a decline in the trading price of our common stock.

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 and security laws apply more broadly than the Health Insurance Portability and Accountability Act (HIPAA) and its implementing regulations. For example, California recently enacted legislation – the California Consumer Privacy Act, or CCPA – effective 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. Further, many data privacy and security laws within the U.S. have concurrent jurisdiction, which could subject us to enforcement by multiple agencies under multiple statutes for the same conduct (e.g., FTC enforcement under Section 5, HHS-Office for Civil Rights enforcement under HIPAA, and actions by state Attorneys General for violation of applicable state laws).

## **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;
- operating and stock price performance of other companies that investors deem comparable to ours;
- recommendations by securities analysts;
- news relating to our industry as a whole and news relating to trends in our markets;
- 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. 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 6, 2020, our executive officers, directors, and 5% stockholders and their affiliates beneficially owned an aggregate of approximately 35% 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 our other stockholders. 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 6, 2020, we have outstanding 37,075,422 shares of common stock and 3,587,523 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, 25,248,097 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 7,481,050 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 2019 public offering and the proceeds from sales pursuant to our 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 2019 public offering and the proceeds from sales pursuant to our December 2019 “at-the-market” sales agreement with SVB Leerink, which provides for the sale of up to \$80.0 million of our common stock from time to time, 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. Our stockholders may not agree with our decisions, and our use of the proceeds may not yield any return on investment for our stockholders. Because of the number and variability of factors that will determine our use of the net proceeds from our Capital Raises their 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. Our stockholders 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 30<sup>th</sup>, and (3) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period. As such, we anticipate that we will no longer be an emerging growth company as of December 31, 2020. 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, 2019, we had U.S. federal net operating loss, NOL, carryforwards of approximately \$154 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 \$94 million generated in 2018 and later have an indefinite carryforward period. Net operating loss carry forwards arising in taxable years ending after December 31, 2017 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, December 2019 public offering, private placements and other transactions that have occurred, may trigger, or may have already triggered, such an ownership change. In addition, since we may need to raise 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, returns for our stockholders 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. In addition, the terms of our existing credit facility with SVB and WestRiver preclude us from paying cash dividends without SVB's and WestRiver's consent. 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. We do not currently have any preferred stock outstanding. 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 200 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.**

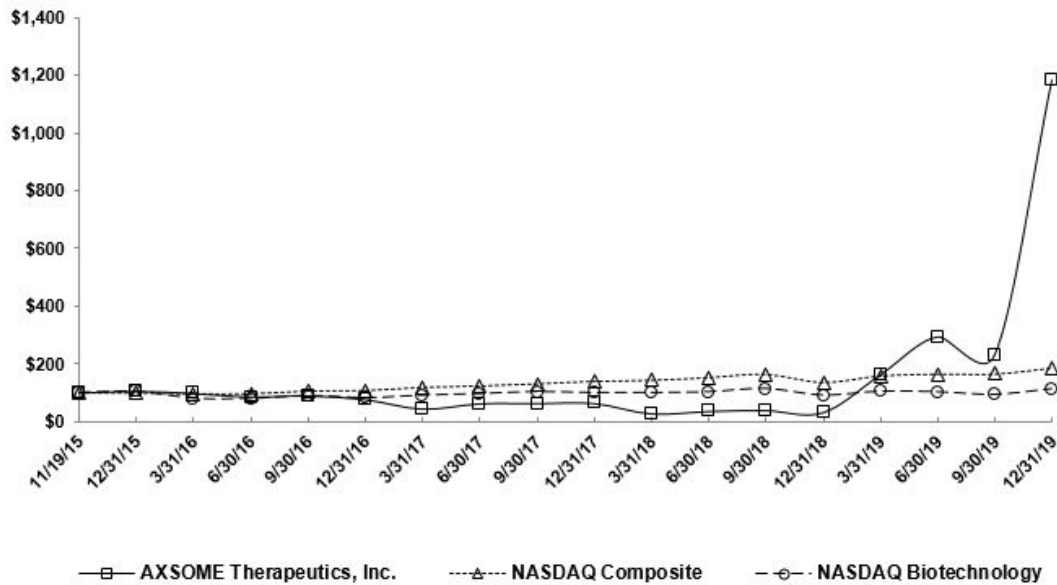
***Market Information***

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, 2019 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.

**COMPARISON OF 49 MONTH CUMULATIVE TOTAL RETURN\***  
 Among AXSOME Therapeutics, Inc., the NASDAQ Composite Index  
 and the NASDAQ Biotechnology Index



\*\$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 6, 2020 was 16. 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, 2019, 2018, and 2017 and Balance Sheet Data as of December 31, 2019, 2018, and 2017, 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,		
	2019	2018	2017
<b>Statements of operations data:</b>			
Operating expenses:			
Research and development	\$ 53,647,067	\$ 23,495,055	\$ 19,957,616
General and administrative	13,598,030	9,351,522	7,206,691
Total operating expenses	<u>67,245,097</u>	<u>32,846,577</u>	<u>27,164,307</u>
Loss from operations	(67,245,097)	(32,846,577)	(27,164,307)
Interest and amortization of debt discount expense	(1,239,537)	(1,127,305)	(1,340,199)
Tax credit	139,448	217,418	207,114
Change in fair value of warrant liability	—	2,791,000	(646,000)
Net loss	<u>\$ (68,345,186)</u>	<u>\$ (30,965,464)</u>	<u>\$ (28,943,392)</u>
Weighted average common shares outstanding—basic and diluted	<u>34,020,257</u>	<u>26,883,656</u>	<u>22,764,606</u>
Net loss per common share—basic and diluted	<u>\$ (2.01)</u>	<u>\$ (1.15)</u>	<u>\$ (1.27)</u>

	As of December 31,		
	2019	2018	2017
<b>Balance sheet data:</b>			
Cash	\$ 219,966,167	\$ 13,968,742	\$ 34,021,123
Total assets	220,549,760	15,379,279	35,555,564
Total current liabilities	24,494,745	10,821,938	12,175,336
Loan payable, long-term, net of discounts	17,332,626	3,619,420	6,663,005
Accumulated deficit	(175,895,493)	(107,550,307)	(76,584,843)
Total stockholders' equity	<u>\$ 178,722,389</u>	<u>\$ 937,921</u>	<u>\$ 16,717,223</u>

## 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 five CNS product candidates, AXS-05, AXS-07, AXS-09, AXS-12, and AXS-14 which are being developed for multiple indications. AXS-05 is currently in a Phase 3 trial in treatment resistant depression, or TRD, which we refer to as the STRIDE-1 study, a Phase 3 open-label safety trial in patients with TRD and major depressive disorder, or MDD, and a Phase 2/3 trial in agitation associated with Alzheimer's disease, or AD, which we refer to as the ADVANCE-1 study. For AXS-05, we have completed a Phase 2 trial and Phase 3 trial in MDD, which we refer to as the ASCEND study and the GEMINI study, respectively. We plan to file a New Drug Application, or NDA, for AXS-05 for the treatment of MDD based on the ASCEND and GEMINI trials. AXS-05 is also being developed for smoking cessation and a Phase 2 trial in the indication has been completed. AXS-07 is currently in a Phase 3 trial for the acute treatment of migraine, which we refer to as the INTERCEPT study and a Phase 3 open-label safety trial in patients with migraine. For AXS-07, we have completed a Phase 3 trial for the acute treatment of migraine, which we refer to as the MOMENTUM study. We plan to file an NDA for AXS-07 for the acute treatment of migraine based on the MOMENTUM trial. AXS-09 is being developed for the treatment of CNS disorders. AXS-12 is being developed for the treatment of narcolepsy. We have completed a Phase 2 trial, which we refer to as the CONCERT study. AXS-14 is being developed for the treatment of fibromyalgia. Additionally, we are currently evaluating other product candidates, which we intend to develop for CNS disorders. The Axsome Pain and Primary Care business unit, or Axsome PPC, houses our pain and primary care assets. 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 a proprietary formulation and dose of bupropion and dextromethorphan, or DM, and utilizes our metabolic inhibition technology. We are developing AXS-05 initially for the following four indications: MDD, TRD, agitation associated with AD, 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, rapidly absorbed, multi-mechanistic, investigational medicine. AXS-07 consists 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<sub>1B/D</sub> 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 NMDA receptor antagonist with multimodal activity 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. AXS-12 has been granted Orphan Drug Designation by the FDA for the treatment of narcolepsy.

AXS-14, esreboxetine, is a novel, oral, investigational medicine in development for the treatment of fibromyalgia. AXS-14 is a highly selective and potent norepinephrine reuptake inhibitor. We are initially developing esreboxetine for the treatment of fibromyalgia. Esreboxetine, the SS-enantiomer of reboxetine, is more potent and selective than racemic reboxetine.

The Axsome Pain and Primary Care business unit, or Axsome PPC, houses our pain and primary care assets, and includes intellectual property which covers these and related product candidates and molecules being developed by us and others.

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 \$68.3 million, \$31.0 million, and \$28.9 million for the years ended December 31, 2019, 2018, and 2017, respectively. Our accumulated deficit as of December 31, 2019 was \$175.9 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 additional 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, 2019, 2018, and 2017:

	Year ended December 31,		
	2019	2018	2017
AXS-05	\$24,786,783	\$ 13,460,809	\$ 9,780,593
AXS-07	20,925,324	3,222,208	180,255
AXS-12	1,823,060	193,459	—
AXS-02	503,244	740,341	6,775,736
AXS-06	8,126	71,164	480,425
Other research and development	4,016,365	5,415,127	2,126,978
Stock-based compensation	1,584,165	391,946	613,629
Total research and development expenses	<u>\$53,647,067</u>	<u>\$ 23,495,055</u>	<u>\$19,957,616</u>

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 December 31, 2017 and 2019, a majority of employee salaries and benefits were allocated between the respective programs in the table above.

#### **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 term loan with SVB (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 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, 2019, we do not believe any material uncertain tax positions are present.

As of December 31, 2019, we had U.S. federal net operating loss, or NOL carryforwards of approximately \$154 million. NOLs amounting to \$60 million generated before the 2018 tax year will start expiring beginning 2033, and the NOLs of approximately \$94 million generated in 2018 and later have an indefinite carryforward period.

Utilization of the NOLs 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.

### ***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, 2019 and 2018**

The following table summarizes our results of operations for the years ended December 31, 2019 and 2018:

	Year ended December 31,	
	2019	2018
Operating expenses:		
Research and development	\$ 53,647,067	\$ 23,495,055
General and administrative	13,598,030	9,351,522
Total operating expenses	67,245,097	32,846,577
Loss from operations	(67,245,097)	(32,846,577)
Interest and amortization of debt discount expense	(1,239,537)	(1,127,305)
Tax credit	139,448	217,418
Change in fair value of warrant liability	—	2,791,000
Net loss	\$ (68,345,186)	\$ (30,965,464)

*Research and Development Expenses.* Our research and development expenses for the year ended December 31, 2019 were \$53.6 million, compared to \$23.5 million for the year ended December 31, 2018, an increase of \$30.1 million. This increase was primarily due to trials that were initiated and completed in 2019, which include the GEMINI, MOMENTUM, and CONCERT trials, along with the initiation of the INTERCEPT and AXS-05 and AXS-07 open-label safety studies in 2019. Additionally, this amount includes ongoing spend for our previously initiated clinical trials, which include STRIDE-1 and ADVANCE-1.

*General and Administrative Expenses.* Our general and administrative expenses for the year ended December 31, 2019 were \$13.6 million, compared to \$9.4 million for the year ended December 31, 2018, an increase of \$4.2 million. The change was primarily due to personnel costs, mainly associated with an increase in stock compensation expense, along with the build-out of the commercial function.

*Interest and Amortization of Debt Discount Expense.* Interest and amortization of debt discount expense for the year ended December 31, 2019 was \$1.2 million, compared to \$1.1 million for the year ended December 31, 2018, an increase of \$0.1 million. The increase was primarily related to higher interest expense and amortization of the debt discount associated with our March 2019 loan and security agreement with SVB for \$20 million, offset by interest income from our cash sweep account.

*Tax Credit.* Tax credit income for the year ended December 31, 2019 was \$0.1 million, as compared to \$0.2 million for the year ended December 31, 2018, a decrease of \$0.1 million. This represents the receipt by Axsome Therapeutics Australia PTY LTD, our Australian subsidiary, of the Australia Tax Incentive Credit related to the 2018 and 2017 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 in 2018 is due to the decrease of our closing stock price over the course of the year, from when the warrants were initially issued in December 2017. These warrants expired in December 2018.

**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:

	<b>Year ended December 31,</b>	
	<b>2018</b>	<b>2017</b>
<b>Operating expenses:</b>		
Research and development	\$ 23,495,055	\$ 19,957,616
General and administrative	9,351,522	7,206,691
Total operating expenses	<u>32,846,577</u>	<u>27,164,307</u>
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	<u><b>\$ (30,965,464)</b></u>	<u><b>\$ (28,943,392)</b></u>

*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.

## Liquidity and Capital Resources

Since our inception through December 31, 2019, we have financed our operations primarily through proceeds from equity offerings and debt borrowings. See discussion below.

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, completed a registered direct offering priced at the market in December 2017 and September 2018, entered into a sales agreement in May 2019 pursuant to which we sold shares of our common stock from time to time in an at-the-market offering 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 now known as SVB Leerink, pursuant to which we could sell up to \$30 million in shares of our common stock from time to time through SVB Leerink, acting as our sales agent, in one or more at-the-market offerings. 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 this final sale, the Sales Agreement was automatically terminated. SVB 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.

In September 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 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 estimated 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.

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.

In May 2019, we entered into the May 2019 Sales Agreement with SVB Leerink, pursuant to which we may sell up to \$50 million in shares of our common stock from time to time through SVB Leerink, acting as our sales agent, in one or more at-the-market offerings utilizing the 2016 Shelf Registration Statement. SVB Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the May 2019 Sales Agreement. We received approximately \$20.1 million in gross proceeds through the sale of 942,285 shares, of which net proceeds were approximately \$19.5 million during the year ended December 31, 2019. Due to expiration of the 2016 Shelf Registration Statement, at our option, the shares that were unsold under the May 2019 Sales Agreement, may be rolled over to the December 2019 Sales Agreement (see below).

In July 2019, we entered into the first amendment to the 2019 Term Loan, or the First Amendment to the 2019 Term Loan. Under the First Amendment to the 2019 Term Loan, the interest-only monthly payment period of the 2019 Term Loan was extended to 18 months after the date of the 2019 Term Loan, which may be further extended to 24 months upon receipt by us of the Term B Loan Advance. Our ability to draw down the Term B Loan Advance was extended to December 31, 2019, subject to our achievement of the Milestone Event prior to or on December 31, 2019. The Loan Advances mature on February 1, 2023. See the subsection titled “July 2019 First Amendment to Loan and Security Agreement – Silicon Valley Bank” under the “Contractual Obligations and Commitments” section below for a further description of the First Amendment to the 2019 Term Loan.

On December 5, 2019, we filed an automatic shelf registration statement with the SEC for the issuance of common stock, preferred stock, warrants, rights, debt securities and units up to an unlimited amount, which we refer to as the 2019 Shelf Registration Statement. It was declared effective by the SEC upon filing. As discussed in greater detail below, we entered into a sales agreement in December 2019 pursuant to which we sold shares of our common stock from time to time in an at-the-market offering and completed an offering of common stock in December 2019, each utilizing the 2019 Shelf Registration Statement. In the future, we may conduct additional offerings of one or more of these securities utilizing the 2019 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 2019 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 December 2019, we entered into the December 2019 Sales Agreement with SVB Leerink, pursuant to which we may sell up to \$80 million in shares of our common stock from time to time through SVB Leerink, acting as our sales agent, in one or more at-the-market offerings utilizing the 2019 Shelf Registration Statement. SVB Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the December 2019 Sales Agreement. We received approximately \$7.3 million in gross proceeds through the sale of 89,390 shares, of which net proceeds were approximately \$7.1 million during the quarter ended December 31, 2019.

In December 2019, we completed an underwritten public offering, whereby we sold 2,300,000 shares of our common stock at a public offering price of \$87.00 per share. We received gross proceeds of approximately \$200.1 million and net proceeds of approximately \$187.1 million, net of underwriting discounts and offering expenses.

We believe our current cash will be sufficient to fund our anticipated operating cash requirements for at least two years. 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,		
	2019	2018	2017
Net cash (used in) provided by:			
Operating activities	\$ (46,375,059)	\$ (30,053,701)	\$ (26,471,652)
Investing activities	(16,121)	(32,696)	(9,898)
Financing activities	252,388,605	10,034,016	23,884,176
Net increase (decrease) in cash	<u>\$ 205,997,425</u>	<u>\$ (20,052,381)</u>	<u>\$ (2,597,374)</u>

*Operating Activities.* Net cash used in operating activities for the year ended December 31, 2019 was \$46.4 million as compared to \$30.1 million for the year ended December 31, 2018. The increase of \$16.3 million in net cash used was primarily related to higher research and development spend related to multiple product candidates in clinical trials.

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.

*Investing Activities.* Cash used in investing activities for the purchase of equipment was less than \$0.1 million for the year ended December 31, 2019, 2018, and 2017.

*Financing Activities.* Net cash provided by financing activities for the year ended December 31, 2019 was \$252.4 million, which includes net proceeds from the sale of common stock in the December 2019 public offering of \$187.1 million, \$51.6 million in proceeds from sales made through at-the-market offerings, \$1.4 million from the exercise of options and warrants, and \$20.0 million in proceeds from our March 2019 term loan which was partially offset by principal repayment on our term loan of \$7.2 million.

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.

## **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, 2019:

(in thousands)	Total	Less than one year	1 - 3 years	3 - 5 years	More than 5 years
Term loan	\$22,982,083	\$4,166,389	\$17,469,444	\$1,346,250	\$ —
Total contractual obligations	\$22,982,083	\$4,166,389	\$17,469,444	\$1,346,250	\$ —

*License agreements with Antecip Bioventures*

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.”

### *License agreement with Pfizer*

Subsequent to December 31, 2019, we entered into a license agreement with Pfizer. Under the terms of our exclusive license agreement with Pfizer, Pfizer received 82,019 shares of our common stock having a value of \$8 million, based on the average closing price of the Company’s common stock for the 10 prior trading days of \$97.538, in consideration for the license and rights. Pfizer also received an upfront cash payment of \$3 million and will also receive up to \$323 million upon the achievement of certain regulatory and sales milestones, and tiered mid-single to low double-digit royalties on future sales. Pfizer will also have a right of first negotiation on any potential future strategic transactions involving AXS-12 and AXS-14. 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 the 2016 Original Term Loan with SVB and Life Sciences Loans, LLC, 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 2016 Original Term 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 2016 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 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 2016 Original Term Loan with SVB and WestRiver Innovation Lending Fund VIII, L.P, 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. In connection with the 2016 Amended Term Loan, SVB and WestRiver received warrants to purchase an aggregate 15,750 shares of our common stock at an exercise price of \$3.06 per share, which are exercisable for seven years from the date of issuance.

Our obligations under the 2016 Amended Term Loan, along with the ability to draw down on the additional \$4.0 million tranche, were considered to be performed and completed in connection with the establishment of the 2019 Term Loan during March 2019.

#### *March 2019 Loan and Security Agreement—Silicon Valley Bank*

In March 2019, we entered into the 2019 Term Loan with SVB and WestRiver 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 then-existing obligations under our 2016 Amended Term Loan and such obligations are considered to be fully repaid and completed.

The 2019 Term Loan accrues interest 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 and is payable monthly. The 2019 Term Loan initially had an interest-only monthly payment period for twelve months which was extendable 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 and these payments will continue until the maturity date of February 1, 2023. In addition, we were initially required to pay a final payment fee of 6.0% of the principal amount extended to us on the date of repayment of the outstanding loan, which was increased to 6.3% in connection with the First Amendment to the 2019 Term Loan, as described below.

We were initially permitted to prepay all, but not less than all, of the 2019 Term Loan, subject to a prepayment premium of 3.0% of the outstanding principal if prepaid within one year of the effective date of the loan, 2.0% of the outstanding principal if prepaid after the first anniversary of the effective date but on prior to the second anniversary of the effective date, and 1.0% of the outstanding principal if prepaid after the second anniversary of the effective date. The term loan is collateralized by a security interest in all of our assets except intellectual property. Our intellectual property is subject to a negative pledge.

In connection with the 2019 Term Loan, SVB and WestRiver received warrants, or the March 2019 Warrants, to purchase an aggregate 70,000 shares of our common stock at an exercise price of \$8.10 per share, which are exercisable for seven years from the date of issuance. The warrants were to 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, of which 58,332 warrants were immediately exercisable and the remaining 11,668 warrants would be earned upon drawing of the second \$4.0 million tranche under the loan. In connection with the First Amendment to the 2019 Term Loan, the shares of common stock issuable under each of the March 2019 Warrants were fixed at 29,167 shares, as described further below.

We allocated the proceeds of \$20.0 million based on the relative fair values of the debt instrument and the warrant instrument. The relative fair value of the warrants of approximately \$0.4 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 is being amortized to interest expense over the term of the debt.

*July 2019 First Amendment to Loan and Security Agreement—Silicon Valley Bank*

In July 2019, we entered into the First Amendment to the 2019 Term Loan. Under the First Amendment to the 2019 Term Loan, the interest-only monthly payment period of the 2019 Term Loan was extended to 18 months after the date of the 2019 Term Loan, which may be further extended to 24 months upon receipt by us of the Term B Loan Advance. Our ability to draw down the Term B Loan Advance was extended to December 31, 2019, subject to our achievement of the Milestone Event prior to or on December 31, 2019. The Loan Advances mature on February 1, 2023.

Pursuant to the 2019 Term Loan, as amended by the First Amendment to the 2019 Term Loan, following the interest-only payment period, we will begin making monthly payments of principal in equal monthly installments for 30 consecutive months (provided, that, upon the occurrence of the Milestone Event, the repayment schedule will be decreased to 24 consecutive months) and monthly payments of 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 First Amendment to the 2019 Term Loan increased the final payment fee, payable upon our repayment of the Loan Advances from 6.0% to 6.30% of the original principal amount of the Loan Advances.

We may prepay all, but not less than all of the Loan Advances, subject to a prepayment fee of 3.0% of any amount prepaid prior to the first anniversary of July 25, 2019, or the First Amendment Effective Date, 2.0% of the amount prepaid if the prepayment occurs after the first anniversary of the First Amendment Effective Date through and including the second anniversary of the First Amendment Effective Date, or 1.0% of the amount prepaid if the prepayment occurs after the second anniversary of the First Amendment Effective Date, but prior to the Maturity Date. These percentages are unchanged from the original 2019 Term Loan.

In connection with the First Amendment to the 2019 Term Loan, the March 2019 Warrants were amended to fix the number of shares that may be issued upon exercise of each such March 2019 Warrant at 29,167 shares of common stock, and SVB and WestRiver were issued the July 2019 Warrants, which become exercisable only upon funding of the Term B Loan Advance, to purchase 5,750 shares of our common stock at a price per share equal to \$25.71. The July 2019 Warrants replace the portion of the March 2019 Warrants that could originally be earned by SVB and WestRiver upon funding of the Term B Loan Advance. The July 2019 Warrants, if earned, will be exercisable until July 24, 2026 and will be exercised automatically on a net issuance basis if not exercised prior to the expiration date and if the then-current fair market value of one share of our common stock is greater than the exercise price then in effect.

**Shelf Registration Statement**

On December 5, 2019, we filed a Form S-3ASR (File No. 333-235372) with the SEC, or the 2019 Shelf Registration Statement, for the issuance of common stock, preferred stock, warrants, rights, debt securities and units, which became effective immediately upon filing. At the time any of the securities covered by the 2019 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. Furthermore, we anticipate that we will no longer be an emerging growth company as of December 31, 2020.

## **Recent Accounting Pronouncements**

Refer to Note 2 – Summary of Significant Accounting Policies to our consolidated financial statements included in Part IV, Exhibits and Financial Statement Schedules, of this Annual Report on Form 10-K for a discussion of recently issued accounting pronouncements.

## **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 \$220.0 million as of December 31, 2019. 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 and debt agreement, 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, 2019 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, 2019.

## **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, 2019. 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, 2019, 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, 2019. 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, 2019, 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. However, we anticipate that we will be required to include such an attestation report with our next annual report in 2021 for the year ended December 31, 2020.

*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 2020 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 2020 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 2020 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 2020 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 2020 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.

<b>Contents</b>	<b>Page</b>
<a href="#">Report of Independent Registered Public Accounting Firm</a>	F-1
<a href="#">Consolidated Balance Sheets as of December 31, 2019 and 2018</a>	F-2
<a href="#">Consolidated Statements of Operations for the Years Ended December 31, 2019, 2018, and 2017</a>	F-3
<a href="#">Consolidated Statements of Stockholders' Equity for the Years Ended December 31, 2019, 2018, and 2017</a>	F-4
<a href="#">Consolidated Statements of Cash Flows for the Years Ended December 31, 2019, 2018, and 2017</a>	F-5
<a href="#">Notes to the Consolidated Financial Statements</a>	F-6

**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**

	<u>Page</u>
<a href="#">Report of Independent Registered Public Accounting Firm</a>	F-1
<a href="#">Consolidated Balance Sheets as of December 31, 2019 and 2018</a>	F-2
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**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, 2019 and 2018, the related consolidated statements of operations, stockholders’ equity, and cash flows for each of the three years in the period ended December 31, 2019, 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, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, 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 12, 2020

**Axsome Therapeutics, Inc.**  
**Consolidated Balance Sheets**

	<b>December 31,</b>	
	<b>2019</b>	<b>2018</b>
<b>Assets</b>		
Current assets:		
Cash	\$ 219,966,167	\$ 13,968,742
Prepaid and other current assets	413,095	1,246,360
Total current assets	220,379,262	15,215,102
Equipment, net	30,623	51,832
Other assets	139,875	112,345
Total assets	<u>\$ 220,549,760</u>	<u>\$ 15,379,279</u>
<b>Liabilities and stockholders' equity</b>		
Current liabilities:		
Accounts payable	\$ 10,943,325	\$ 3,687,245
Accrued expenses and other current liabilities	10,949,128	3,843,299
Loan payable, current portion	2,602,292	3,291,394
Total current liabilities	24,494,745	10,821,938
Loan payable, long-term	17,332,626	3,619,420
Total liabilities	<u>41,827,371</u>	<u>14,441,358</u>
Stockholders' equity:		
Preferred stock, \$0.0001 par value per share (10,000,000 shares authorized, none issued and outstanding at December 31, 2019 and December 31, 2018, respectively)	—	—
Common stock, \$0.0001 par value per share (150,000,000 shares authorized, 36,933,217 and 30,087,213 shares issued and outstanding at December 31, 2019 and December 31, 2018, respectively)	3,693	3,009
Additional paid-in capital	354,614,189	108,485,219
Accumulated deficit	<u>(175,895,493)</u>	<u>(107,550,307)</u>
Total stockholders' equity	178,722,389	937,921
Total liabilities and stockholders' equity	<u>\$ 220,549,760</u>	<u>\$ 15,379,279</u>

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

**Axsome Therapeutics, Inc.**  
**Consolidated Statements of Operations**

	Year ended December 31,		
	2019	2018	2017
Operating expenses:			
Research and development	\$ 53,647,067	\$ 23,495,055	\$ 19,957,616
General and administrative	13,598,030	9,351,522	7,206,691
Total operating expenses	67,245,097	32,846,577	27,164,307
Loss from operations	(67,245,097)	(32,846,577)	(27,164,307)
Interest and amortization of debt discount expense	(1,239,537)	(1,127,305)	(1,340,199)
Tax credit	139,448	217,418	207,114
Change in fair value of warrant liability	—	2,791,000	(646,000)
Net loss	\$ (68,345,186)	\$ (30,965,464)	\$ (28,943,392)
Net loss per common share, basic and diluted	\$ (2.01)	\$ (1.15)	\$ (1.27)
Weighted average common shares outstanding, basic and diluted	34,020,257	26,883,656	22,764,606

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

**Axsome Therapeutics, Inc.**  
**Consolidated Statements of Stockholders' Equity**

	<u>Common stock</u>			<u>Accumulated deficit</u>	<u>Total stockholders' equity (deficit)</u>
	<u>Shares</u>	<u>Amount</u>	<u>Additional paid- in capital</u>		
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
Issuance of common stock upon 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
Stock-based compensation	—	—	6,115,160	—	6,115,160
Issuance of common stock upon exercise of options	252,773	25	1,143,816	—	1,143,841
Exercise of warrants	97,541	10	249,826	—	249,836
Issuance of warrants upon debt financing	—	—	387,000	—	387,000
Issuance of common stock upon financing	6,495,690	649	238,233,168	—	238,233,817
Net loss	—	—	—	(68,345,186)	(68,345,186)
Balance at December 31, 2019	<u>36,933,217</u>	<u>\$ 3,693</u>	<u>\$ 354,614,189</u>	<u>\$ (175,895,493)</u>	<u>\$ 178,722,389</u>

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

**Axsome Therapeutics, Inc.**  
**Consolidated Statements of Cash Flows**

	Year ended December 31,		
	2019	2018	2017
<b>Cash flows from operating activities</b>			
Net loss	\$ (68,345,186)	\$ (30,965,464)	\$ (28,943,392)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	6,115,160	1,754,974	2,072,210
Amortization of debt discount	649,993	375,635	470,521
Change in fair value of warrants	—	(2,791,000)	646,000
Depreciation	37,330	48,935	42,557
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	833,265	32,058	102,143
Other assets	(27,530)	75,607	(75,131)
Accounts payable	7,256,080	251,789	(645,717)
Accrued expenses and other current liabilities	7,105,829	1,163,765	(140,843)
Net cash used in operating activities	<u>(46,375,059)</u>	<u>(30,053,701)</u>	<u>(26,471,652)</u>
<b>Cash flows from investing activities</b>			
Purchases of equipment	(16,121)	(32,696)	(9,898)
Net cash used in investing activities	<u>(16,121)</u>	<u>(32,696)</u>	<u>(9,898)</u>
<b>Cash flows from financing activities</b>			
Proceeds from issuance of term loan	20,000,000	—	—
Payment of debt issuance costs	—	(25,997)	—
Repayment of principal on term loan	(7,238,889)	(3,333,333)	(277,778)
Proceeds from issuance of common stock upon financing, net	238,233,817	12,881,321	23,677,341
Proceeds from issuance of common stock upon exercise of warrants	249,836	131,703	167,894
Proceeds from issuance of common stock upon exercise of options	1,143,841	380,322	316,719
Net cash provided by financing activities	<u>252,388,605</u>	<u>10,034,016</u>	<u>23,884,176</u>
Net (decrease) increase in cash	<u>205,997,425</u>	<u>(20,052,381)</u>	<u>(2,597,374)</u>
Cash at beginning of period	13,968,742	34,021,123	36,618,497
Cash at end of period	<u>\$ 219,966,167</u>	<u>\$ 13,968,742</u>	<u>\$ 34,021,123</u>
<b>Supplemental disclosures of cash flow information:</b>			
Interest paid	\$ 1,287,506	\$ 771,966	\$ 865,278
<b>Supplemental disclosures of non-cash financing activity:</b>			
Establishment of warrant liabilities in connection with common stock issuance	\$ —	\$ —	\$ 2,145,000
Issuance of warrants in connection with debt financing	\$ 387,000	\$ 37,842	\$ —

*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 five product candidates, AXS-05, AXS-07, AXS-09, AXS-12, and AXS-14 which are being developed for multiple indications. 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, 2019, the Company had an accumulated deficit of \$175.9 million.

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 along with cost to commercialize its product candidates. The Company is dependent upon 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, 2019 and 2018.

## **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, 2019, 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.

## **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, 2019 and 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 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, 2019, 2018, and 2017.

## **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. The Company has adopted this guidance effective January 1, 2019. The Company evaluated its contracts and concluded that the contracts are not leases and do not contain a lease and the adoption of this guidance did not impact its 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 has adopted this guidance effective January 1, 2019 and the adoption of the guidance did not have a material impact on the Company's financial statements.

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 has adopted this guidance effective January 1, 2019 and the adoption of the guidance did not have a material impact on the Company’s financial statements.

In December 2019, the FASB issued ASU 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes* (ASU 2019-12). The new standard simplifies the accounting for income taxes by removing exceptions to the incremental approach for intraperiod tax allocation when there is a loss from continuing operations and income or a gain from other items, to the requirement to recognize a deferred tax liability for equity method investments when a foreign subsidiary becomes an equity method investment, to the ability not to recognize a deferred tax liability for a foreign subsidiary when a foreign equity method investment becomes a subsidiary, and to the general methodology for calculating income taxes in an interim period when a year-to-date loss exceeds the anticipated loss for the year. In addition, the standard requires that an entity recognize a franchise tax that is partially based on income as an income-based tax and account for any incremental amount incurred as a non-income-based tax, evaluate when a step up in the tax basis of goodwill should be considered part of the business combination in which the book goodwill was originally recognized and when it should be considered a separate transaction, reflect the effect of an enacted change in tax laws or rates in the annual effective tax rate computation in the interim period that includes the enactment date, and specifying that an entity is not required to allocate the consolidated amount of current and deferred tax expense to a legal entity that is not subject to tax in its separate financial statements, however, an entity may elect to do so (on an entity-by-entity basis) for a legal entity that is both not subject to tax and disregarded by the taxing authority. ASU 2019-12 is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2020. Early adoption is permitted, including adoption in an interim period. The Company is currently evaluating the expected impact of this standard, but does not expect it to have a material impact on its consolidated financial statements upon adoption.

**Note 3. Fair Value Measurements**

**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 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.

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, 2019.

**Note 4. Net Loss per Common Share**

The following table sets forth the computation of basic and diluted net loss per common share:

	<u>Year ended December 31,</u>		
	<u>2019</u>	<u>2018</u>	<u>2017</u>
Basic and diluted net loss per common share:			
Net loss	\$ (68,345,186)	\$ (30,965,464)	\$ (28,943,392)
Weighted average common shares outstanding—basic and diluted	34,020,257	26,883,656	22,764,606
Net loss per common share—basic and diluted	<u>\$ (2.01)</u>	<u>\$ (1.15)</u>	<u>\$ (1.27)</u>

The following potentially dilutive securities outstanding at December 31, 2019, 2018, and 2017 have been excluded from the computation of diluted weighted average shares outstanding, as they would be anti-dilutive:

	<u>December 31,</u>		
	<u>2019</u>	<u>2018</u>	<u>2017</u>
Stock options	3,458,447	2,291,163	2,315,638
Warrants	69,656	123,037	2,099,199
Total	<u>3,528,103</u>	<u>2,414,200</u>	<u>4,414,837</u>

**Note 5. Accrued Expenses and Other Current Liabilities**

At December 31, 2019 and 2018, accrued expenses consisted of the following:

	<u>December 31,</u>	
	<u>2019</u>	<u>2018</u>
Research and development	\$ 8,209,594	\$ 2,266,285
Accrued compensation	2,056,356	1,051,401
Other	683,178	525,613
Total	<u>\$ 10,949,128</u>	<u>\$ 3,843,299</u>

**Note 6.      Loan and Security Agreement**

*Current Term Loan*

*2019 Term Loan*

In March 2019, the Company entered into a \$24.0 million growth capital term loan facility (the “2019 Term Loan”) with Silicon Valley Bank (“SVB”) and WestRiver Innovation Lending Fund VIII, L.P (“WestRiver”). The two-tranche loan agreement consists of an initial \$20.0 million tranche (the “Term A Loan Advance”), which was funded upon closing, with the remaining \$4.0 million (the “Term B Loan Advance”) initially available to be drawn, at the Company’s option, subject to the achievement of positive data, on or prior to August 15, 2019 (which was extended to December 31, 2019, in connection with the First Amendment to the 2019 Term Loan, as discussed below), 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 (the “Milestone Event”). A portion of the first tranche was used to satisfy the Company’s existing obligations under the 2016 Amended Term Loan (as defined below) with SVB, which consisted of \$5.6 million in outstanding principal balance and \$0.85 million as a final payment fee, and such obligations are considered to be fully repaid and performed. The Term B Loan Advance of \$4.0 million was not drawn down by the Company and has since expired.

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 initially had an interest-only payment period of 12 months (which was extended to 18 months in connection with the First Amendment to the 2019 Term Loan, as discussed below), extendable to 18 months upon the drawing of the Term B Loan Advance (which is now extendable to 24 months as a result of the First Amendment to the 2019 Term Loan). Principal payments coming due within twelve months have been classified as current liabilities in the accompanying balance sheet. In addition, the Company was initially required to pay a final payment fee of 6.0% of the principal amount extended on the date of repayment of the 2019 Term Loan (which was increased to 6.3% in connection with the First Amendment to the 2019 Term Loan, as discussed below), which is being accreted and amortized into interest expense using the effective interest rate method over the term of the loan.

The Company could initially prepay all, but not less than all, of the 2019 Term Loan, subject to a prepayment premium of 3.0% of the outstanding principal if prepaid within one year of the effective date of the loan, 2.0% of the outstanding principal if prepaid after the first anniversary of the effective date but on or prior to the second anniversary of the effective date, and 1.0% of the outstanding principal if prepaid after the second anniversary of the effective date. The 2019 Term Loan is collateralized by a security interest in all of the Company’s assets except intellectual property. The Company’s intellectual property is subject to a negative pledge.

*First Amendment to the 2019 Term Loan*

On July 25, 2019 (the “First Amendment Effective Date”), the Company entered into the first amendment to the 2019 Term Loan (the “First Amendment to the 2019 Term Loan”). Under the First Amendment to the 2019 Term Loan, the interest-only monthly payment period was extended to 18 months after the date of the 2019 Term Loan, which may be further extended to 24 months upon receipt by the Company of the Term B Loan Advance. The Company’s ability to draw down the Term B Loan Advance was extended to December 31, 2019, subject to the Company’s achievement of the Milestone Event prior to or on December 31, 2019. The Term B Loan Advance and the Term A Loan Advance (together, the “Loan Advances”) mature on February 1, 2023 (the “Maturity Date”).

Pursuant to the 2019 Term Loan, as amended by the First Amendment to the 2019 Term Loan, following the interest-only payment period, the Company will begin making monthly payments of principal in equal monthly installments for 30 consecutive months (provided, that, upon the occurrence of the Milestone Event, the repayment schedule will be decreased to 24 consecutive months) and monthly payments of 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 First Amendment to the 2019 Term Loan increased the final payment fee, payable upon the Company's repayment of the Loan Advances from 6.0% to 6.3% of the original principal amount of the Loan Advances.

The Company may prepay all, but not less than all of the Loan Advances, subject to a prepayment fee of 3.0% of any amount prepaid prior to the first anniversary of the First Amendment Effective Date, 2.0% of the amount prepaid if the prepayment occurs after the first anniversary of the First Amendment Effective Date through and including the second anniversary of the First Amendment Effective Date, or 1.0% of the amount prepaid if the prepayment occurs after the second anniversary of the First Amendment Effective Date, but prior to the Maturity Date. These percentages are unchanged from the original 2019 Term Loan.

The Company evaluated whether the First Amendment to the 2019 Term Loan entered into in July 2019 represented a debt modification or extinguishment in accordance with ASC 470-50, Debt – Modifications and Extinguishments. As the present value of the cash flows under the terms of the First Amendment to the 2019 Term Loan is less than 10% different from the remaining cash flows under the terms of the 2019 Term Loan, the First Amendment to the 2019 Term Loan was accounted for as a debt modification. Therefore, the unamortized balance of debt discount costs incurred in connection with 2019 Term Loan are being amortized through maturity in February 2023 utilizing the effective interest rate method.

#### *Previous Term Loan*

Prior to the 2019 Term Loan, the Company had a \$20.0 million Term Loan Agreement with SVB which was executed in November 2016 ("2016 Original Term Loan"). The three-tranche term loan consisted 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 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.

The 2016 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 was extendable to May 2018 upon the drawing of the second tranche. 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. 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 2016 Original Term Loan. The Company accrued the final payment fee into interest expense using the effective interest rate method until the entry into the 2019 Term Loan in March 2019, at which time the Company paid SVB \$0.85 million in satisfaction of all final payment fee liabilities due under the 2016 Original Term Loan.

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 2016 Original Term Loan with SVB to provide an additional \$4.0 million growth capital loan. 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's obligations under the 2016 Amended Term Loan, along with the ability of the Company to draw down on the additional \$4.0 million tranche, were considered performed and completed in connection with the establishment of the 2019 Term Loan.

The Company evaluated whether the 2019 Term Loan entered into in March 2019 represented a debt modification or extinguishment in accordance with ASC 470-50, Debt – Modifications and Extinguishments. As the present value of the cash flows under the terms of the 2019 Term Loan is less than 10% different from the remaining cash flows under the terms of the 2016 Original Term Loan and the 2016 Amended Term Loan, the 2019 Term Loan was accounted for as a debt modification. Since the borrowing capacity of the 2019 Term Loan is greater than the borrowing capacity from the 2016 Original Term Loan and the 2016 Amended Term Loan, the unamortized balance of debt discount costs incurred in connection with those loans and additional debt discount costs incurred in connection with entry into the 2019 Term Loan, are being amortized through maturity in February 2023 utilizing the effective interest rate method.

The book value of debt approximates its fair value given its short term maturity and variable interest rate. Interest expense was \$1,362,500, \$751,670, and \$869,678 and amortization of the final payment was \$436,567, \$266,668, and \$346,978 for the years ended December 31, 2019, 2018, and 2017, respectively.

Long-term debt and unamortized debt discount balances are as follows:

	<u>December 31, 2019</u>	<u>December 31, 2018</u>
Outstanding principal amount	\$ 20,000,000	\$ 6,388,889
Add: accreted liability of final payment fee	404,364	663,459
Less: unamortized debt discount, long term	(405,071)	(99,595)
Less: current portion of long-term debt	(2,666,667)	(3,333,333)
Loan payable, long-term	<u>\$ 17,332,626</u>	<u>\$ 3,619,420</u>
Current portion of outstanding principal amount	2,666,667	3,333,333
Less: current portion of unamortized debt discount	(64,375)	(41,939)
Loan payable, current portion	<u>\$ 2,602,292</u>	<u>\$ 3,291,394</u>

Further information on warrants issued related to the debt financings and amendments are disclosed in Note 8 - Warrants.

Amortization of the debt discount in relation to warrants issued in Note 8 - Warrants was \$213,426, \$108,968, and \$123,543 for the year ended December 31, 2019, 2018, and 2017, respectively. Due to the debt modification upon entry of the 2019 Term Loan, the unamortized balance of the deferred debt issuance costs incurred with the 2016 Amended Term Loan will continue to be amortized through maturity in February 2023 along with the debt issuance costs of the 2019 Term Loan utilizing the effective interest rate method.

Scheduled Principal Payments on Outstanding Debt, as of December 31, 2019, are as follows:

2020	\$	2,666,667
2021		8,000,000
2022		8,000,000
2023		1,333,333
Total principal payments outstanding	\$	<u>20,000,000</u>

## Note 7. Stockholders' Equity

### Capital Structure

In October 2017, the Company entered into the Sales Agreement with SVB Leerink, pursuant to which the Company may sell up to \$30 million in shares of its common stock from time to time through SVB Leerink, acting as its sales agent, in one or more at-the-market offerings. 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 this final sale, the Sales Agreement was automatically terminated, SVB 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.

In May 2019, the Company entered into the May 2019 Sales Agreement with SVB Leerink, pursuant to which the Company may sell up to \$50 million in shares of the Company's common stock from time to time through SVB Leerink, acting as the Company's sales agent, in one or more at-the-market offerings utilizing the 2016 Shelf Registration Statement. SVB Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the May 2019 Sales Agreement. The Company received approximately \$20.1 million in gross proceeds through the sale of 942,285 shares, of which net proceeds were approximately \$19.5 million during the year ended December 31, 2019. Due to expiration of the 2016 Shelf Registration Statement, at the Company's option, the shares that were unsold under the May 2019 Sales Agreement, may be rolled over to the December 2019 Sales Agreement (see below).



In December 2019, the Company entered into the December 2019 Sales Agreement with SVB Leerink, pursuant to which the Company may sell up to \$80 million in shares of the Company's common stock from time to time through SVB Leerink, acting as the Company's sales agent, in one or more at-the-market offerings utilizing the 2019 Shelf Registration Statement. SVB Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the December 2019 Sales Agreement. The Company received approximately \$7.3 million in gross proceeds through the sale of 89,390 shares, of which net proceeds were approximately \$7.1 million during the quarter ended December 31, 2019.

In December 2019, the Company completed an underwritten public offering, whereby the Company sold 2,300,000 shares of our common stock at a public offering price of \$87.00 per share. The Company received gross proceeds of approximately \$200.1 million and net proceeds of approximately \$187.1 million, net of underwriting discounts and offering expenses.

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 5, 2019, the Company filed an automatic shelf registration statement ("2019 Shelf Registration") with the Securities and Exchange Commission ("SEC") for the issuance of common stock, preferred stock, warrants, rights, debt securities and units. It became effective upon filing with the SEC and is currently the Company's only active shelf registration. Through the date of this report, the Company has issued common stock of approximately \$207.4 million pursuant to such shelf registration statement.

In the future, the Company may also periodically offer unlimited number 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 2019 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, 2019, there were 3,388,926 shares available for future grant under the 2015 Plan.

## Stock Options

The following table summarizes stock option activity as of December 31, 2019:

	Number of shares	Weighted average exercise price	Weighted average contractual term	Aggregate intrinsic value
Outstanding at December 31, 2018	2,282,636	5.06		
Granted	1,484,352	17.00		
Exercised	(252,773)	4.53		
Forfeited	(55,768)	7.26		
Expired	—	—		
Outstanding at December 31, 2019	<u>3,458,447</u>	<u>10.19</u>	<u>8.0</u>	<u>322,229,820</u>
Vested and expected to vest at December 31, 2019	<u>3,449,778</u>	<u>10.21</u>	<u>8.0</u>	<u>321,347,251</u>
Exercisable at December 31, 2019	<u>1,861,890</u>	<u>7.23</u>	<u>6.5</u>	<u>178,992,676</u>

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, 2019, 2018, and 2017 is as follows:

<u>Black-Scholes option valuation assumptions</u>	<u>2019</u>	<u>2018</u>	<u>2017</u>
Risk-free interest rates	1.4 - 2.7 %	2.0 - 3.1 %	1.6 - 2.2 %
Dividend yield	—	—	—
Volatility	87 - 91 %	74 - 87 %	73 - 77 %
Weighted average expected term	5.00 - 6.13 years	3.66 - 6.13 years	3.50 - 6.12 years

The weighted average grant date fair value of options granted was \$12.49, \$1.99, and \$3.06 per option for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, there was \$14.9 million of total unrecognized compensation cost related to non-vested stock options which is expected to be recognized over a weighted average period of 3.3 years. These amounts do not include 15,269 options outstanding as of December 31, 2019, which are performance-based and vest upon the achievement of certain corporate milestones. 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, 2019, 2018, and 2017 was as follows:

	2019	2018	2017
Research and development	\$ 1,584,165	\$ 391,946	\$ 613,629
General and administrative	4,530,995	1,363,028	1,458,581
Total	\$ 6,115,160	\$ 1,754,974	\$ 2,072,210

#### Performance-Based Awards

During the year ended December 31, 2019, the Company issued 4,500 performance-based awards at an exercise price of \$16.71, to employees that vest upon completion of certain clinical events. 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, 2019, 2018, and 2017, the Company recognized \$88,835, \$1,587, and \$59,424, respectively, as expense related to performance-based awards.

**Note 8. Warrants**

As of December 31, 2019, the Company had outstanding warrants to purchase 69,656 shares of common stock. The following table summarizes warrant activity as of December 31, 2019, 2018, and 2017:

	Warrants	Weighted average exercise price
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
Issued	58,334	8.10
Exercised	(111,715)	6.73
Outstanding at December 31, 2019	69,656	\$ 7.21

In connection with the Company's new term loan facility with SVB and WestRiver which was completed in March 2019, the Company issued warrants for up to 70,000 shares of the Company's common stock at a price per share equal to \$8.10 based upon usage of the facility and are exercisable until March 4, 2026. The warrants were classified as a component of stockholders' equity. On July 25, 2019, in connection with the First Amendment to the 2019 Term Loan, the March 2019 Warrants were amended to fix the number of shares that may be issued upon exercise of each such March 2019 Warrant at 29,167 shares of common stock, and SVB and WestRiver were issued new warrants (the "July 2019 Warrants"), which would have become exercisable upon funding of the Term B Loan Advance, to purchase 5,750 shares of the Company's common stock at a price per share equal to \$25.71. The July 2019 Warrants replace the portion of the March 2019 Warrants that could originally be earned by SVB and WestRiver upon funding of the Term B Loan Advance. Due to the Company not drawing down on the Term B Loan Advance by December 31, 2019, the July 2019 Warrants have been terminated. In December 2019, SVB exercised in full its portion of 29,167 warrants it received in connection with the 2019 Term Loan via a cashless exercise. The Company issued SVB 24,185 shares of its common stock in connection with the warrant exercise and did not receive any cash proceeds. As of December 31, 2019, WestRiver's portion of 29,167 warrants remain outstanding.

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. In August 2019, SVB exercised in full its portions of 7,875 warrants it received in connection with the 2016 Amended Term Loan via a cashless exercise. The Company issued SVB 6,969 shares of its common stock in connection with the warrant exercise, and did not receive any cash proceeds. The 2018 warrants have a seven-year term and expire on November 25, 2025. As of December 31, 2019, WestRiver's portion of 7,875 warrants remain outstanding.

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”) to SVB and Life Sciences. The warrants were classified as a component of stockholders' equity. In September 2019, SVB exercised its portion of 32,614 warrants it received in connection with the 2016 Original Term Loan via a cashless exercise. The Company issued SVB 24,328 shares of its common stock in connection with the warrant exercise, and did not receive any cash proceeds. The 2016 warrants have a seven-year term and expire on November 8, 2023. As of December 31, 2019, Life Sciences portion of 32,164 warrants remain outstanding.

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 had a five-year term and an expiration of November 2, 2019. All 42,059 warrants were exercised in 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:

<b>Black-Scholes option valuation assumptions</b>	<b>2019 warrants</b>	<b>2018 warrants</b>	<b>2017 warrants</b>	<b>2016 warrants</b>	<b>2014 warrants</b>	<b>2013 warrants</b>
Risk-free interest rate	2.8 %	3.0 %	1.7 %	1.8 %	1.6 %	1.4 %
Dividend yield	—	—	—	—	—	—
Volatility	97 %	85 %	61 %	73 %	70 %	64 %
Weighted average contractual term	7 years	7 years	1 year	7 years	5 years	5 years

## **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.

In January 2020, the Company entered into an exclusive license agreement with Pfizer Inc. See Note 14 – Subsequent Event, for further information.

## **Note 10. Commitments and Contingencies**

### **Operating Leases**

The Company's offices are located in New York, New York. The Company is currently under a short-term lease agreement, which does not qualify for accounting under ASC 842. Rent expense incurred during the years ended December 31, 2019, 2018 and 2017 was \$485,548, \$315,301, and \$307,557.

## **Note 11. Income Taxes**

As of December 31, 2019, the Company has U.S. federal net operating loss ("NOL") carryforwards of approximately \$154 million. NOLs amounting to \$60 million generated before the 2018 tax year will start expiring beginning 2033, and the NOL of approximately \$94 million generated in 2018 and later have 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 and deferred tax liabilities are as follows:

	<u>December 31, 2019</u>	<u>December 31, 2018</u>
<b>Deferred tax assets:</b>		
Net federal operating loss carryforward	\$ 32,299,085	\$ 18,911,435
Net foreign operating loss carryforward	59,557	40,927
Net state operating loss carryforward	20,000,317	11,842,460
Non-cash compensation	3,485,519	1,625,560
Research and development credits	10,366,683	7,651,781
Deferred finance costs	—	38,578
Interest Expense	985,431	400,946
Charitable Contribution	5,408	5,408
Fixed Assets	11,401	8,595
Accrued expenses	1,200,754	732,958
Deferred tax asset, excluding valuation allowance	<u>68,414,155</u>	<u>41,258,648</u>
<b>Deferred tax liabilities:</b>		
Deferred finance costs	<u>(121,875)</u>	<u>—</u>
Deferred tax liability, excluding valuation allowance	<u>(121,875)</u>	<u>—</u>
Less valuation allowance	<u>(68,292,280)</u>	<u>(41,258,648)</u>
<b>Net deferred tax assets</b>	<b><u>\$ —</u></b>	<b><u>\$ —</u></b>

A valuation allowance is provided for deferred tax assets where the recoverability of the assets is uncertain. The determination to provide a valuation allowance is dependent upon the assessment of whether it is more likely than not that sufficient future taxable income will be generated to utilize the deferred tax assets. Based on the weight of the available evidence, which includes the Company's historical operating losses and forecast of future losses, the Company provided a full valuation allowance against the deferred tax assets resulting from the tax loss and credits carried forward. Valuation allowance increased \$27.0 million, \$12.5 million, and \$6.7 million, in 2019, 2018, and 2017, 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, 2019, 2018, and 2017. 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:

	<u>December 31, 2019</u>	<u>December 31, 2018</u>	<u>December 31, 2017</u>
U.S. federal statutory income tax rate	21.0 %	21.0 %	34.0 %
State taxes, net of federal benefit	13.5	13.1	10.0
Stock based compensation - Excess tax benefit	1.2	1.1	(1.0)
Other permanent differences	(0.1)	(1.3)	(1.9)
Tax credit	4.2	6.3	7.7
US Federal tax rate change - tax reform	—	—	(25.4)
Change in valuation allowance	<u>(39.8)</u>	<u>(40.2)</u>	<u>(23.4)</u>
Effective tax rate	<u>— %</u>	<u>— %</u>	<u>— %</u>

The Company is not currently under examination at the federal or state levels and as of the date of the consolidated financial statements, and 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.

**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 – License Agreements for further information regarding the license agreements.

**Note 13. Quarterly Consolidated Financial Data (Unaudited)**

	2019			
	Mar. 31	June 30	Sept. 30	Dec. 31
Total operating expenses	\$ 10,421,473	\$ 13,448,219	\$ 18,947,235	\$ 24,428,170
Net loss	\$ (10,640,376)	\$ (13,762,214)	\$ (19,135,612)	\$ (24,806,984)
Net loss per common share, basic and diluted (1)	\$ (0.32)	\$ (0.41)	\$ (0.56)	\$ (0.71)

	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)

- (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 Event**

In January 2020, the Company entered into an exclusive license agreement with Pfizer Inc. for Pfizer's clinical and nonclinical data, and intellectual property for reboxetine, the active pharmaceutical ingredient in AXS-12 which the Company is developing for the treatment of narcolepsy. The agreement also provides the Company exclusive rights to develop and commercialize esreboxetine, a new late-stage product candidate now referred to as AXS-14, in the U.S. for the treatment of fibromyalgia.

Under the terms of the Agreement, Pfizer received 82,019 shares of the Company's common stock having a value of \$8 million, based on the average closing price of the Company's common stock for the 10 prior trading days of \$97.538, in consideration for the license and rights. Pfizer also received an upfront cash payment of \$3 million and will also receive up to \$323 million in regulatory and sales milestones, and tiered mid-single to low double-digit royalties on future sales. Pfizer will also have a right of first negotiation on any potential future strategic transactions involving AXS-12 and AXS-14.



## INDEX EXHIBITS

<b>Exhibit Number</b>	<b>Description</b>
3.1	<a href="#">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.)</a>
3.2	<a href="#">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.)</a>
4.1	<a href="#">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.)</a>
4.2	<a href="#">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.)</a>
4.3	<a href="#">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.)</a>
4.4	<a href="#">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.)</a>
4.5	<a href="#">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.)</a>
4.6	<a href="#">Form of Warrant (Incorporated by reference, Exhibit 4.1 to the Company's Current Report on Form 8-K filed December 4, 2017.)</a>
4.7	<a href="#">Warrant to Purchase Stock made by the Company in favor of Silicon Valley Bank, dated March 5, 2019, as amended (Incorporated by reference, Exhibit 10.2 to the Company's Current Report on Form 8-K filed July 29, 2019).</a>
4.8	<a href="#">Warrant to Purchase Stock made by the Company in favor of WestRiver Innovation Lending Fund VIII, L.P., dated March 5, 2019, as amended (Incorporated by reference, Exhibit 10.3 to the Company's Current Report on Form 8 K filed July 29, 2019).</a>
4.9	<a href="#">Warrant to Purchase Stock made by the Company in favor of Silicon Valley Bank, dated July 25, 2019 (Incorporated by reference, Exhibit 10.4 to the Company's Current Report on Form 8 K filed July 29, 2019).</a>
4.10	<a href="#">Warrant to Purchase Stock made by the Company in favor of WestRiver Innovation Lending Fund VIII, L.P., dated July 25, 2019 (Incorporated by reference, Exhibit 10.5 to the Company's Current Report on Form 8- K filed July 29, 2019).</a>
4.11	<a href="#">Form of Warrant, with respect to November 2018 First Amendment to Loan and Security Agreement (Incorporated by reference, Exhibit 4.7 to the Company's Annual Report on Form 10-K, filed March 15, 2019).</a>
4.12	<a href="#">Form of Warrant, with respect to March 2019 Loan and Security Agreement (Incorporated by reference, Exhibit 4.8 to the Company's Annual Report on Form 10-K, filed March 15, 2019).</a>
4.13**	<a href="#">Description of Securities.</a>
10.1+	<a href="#">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.)</a>
10.2+	<a href="#">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.)</a>
10.3+	<a href="#">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.)</a>

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- 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 [Form of Purchase Agreement, dated as of November 30, 2017 among Axsome Therapeutics, Inc. and the purchasers thereunder \(Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K filed December 4, 2017.\)](#)
  - 10.10+ [Nick Pizzie Offer Letter, dated April 16, 2018 \(Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed May 8, 2018.\)](#)
  - 10.11 [Form of Purchase Agreement, dated as of September 27, 2018, by and among the Company and the investors party thereto \(Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K, filed September 28, 2018.\)](#)
  - 10.12 [First Amendment to Loan and Security Agreement, dated as of November 26, 2018, by and between the Company and Silicon Valley Bank \(Incorporated by reference, Exhibit 10.14 to the Company's Annual Report on Form 10-K, filed March 15, 2019\).](#)
  - 10.13 [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. \(Incorporated by reference, Exhibit 10.14 to the Company's Annual Report on Form 10-K, filed March 15, 2019\).](#)
  - 10.14 [First Amendment to Loan and Security Agreement dated as of July 25, 2019 by and among the Company, Silicon Valley Bank, in its capacity as administrative agent and collateral agent, Silicon Valley Bank, as a lender, WestRiver Innovation Lending Fund VIII, L.P., as a lender and each of the other lenders from time to time party thereto \(Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K, filed July 29, 2019\).](#)
  - 10.15\*\*++ [License Agreement, dated as of January 10, 2020, by and between the Company and Pfizer Inc.](#)
  - 10.16 [Share Transfer Agreement by and between the Company and Pfizer Inc. \(Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K, filed January 13, 2019\).](#)
  - 10.17\*\* [Axsome Therapeutics, Inc. Form of Restricted Stock Unit Agreement pursuant to the 2015 Omnibus Incentive Compensation Plan.](#)
  - 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 \(furnished herewith\).](#)
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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.

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+ 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.

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**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 12<sup>th</sup> day of March 2020.

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:

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>          /s/ Herriot Tabuteau, M.D.</u> Herriot Tabuteau, M.D.	Chief Executive Officer and Chairman of the Board (Principal Executive Officer)	March 12, 2020
<u>          /s/ Nick Pizzie</u> Nick Pizzie	Chief Financial Officer (Principal Financial and Accounting Officer)	March 12, 2020
<u>          /s/ Roger Jeffs, Ph.D.</u> Roger Jeffs, Ph.D.	Director	March 12, 2020
<u>          /s/ Mark Coleman, M.D.</u> Mark Coleman, M.D.	Director	March 12, 2020
<u>          /s/ Mark Saad</u> Mark Saad	Director	March 12, 2020
<u>          /s/ Myrtle Potter</u> Myrtle Potter	Director	March 12, 2020

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**DESCRIPTION OF THE REGISTRANT'S SECURITIES  
REGISTERED PURSUANT TO SECTION 12 OF THE  
SECURITIES EXCHANGE ACT OF 1934**

The following description sets forth certain material terms and provisions of our securities that are registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). This description also summarizes relevant provisions of the General Corporation Law of Delaware (the "DGCL"). The following description is a summary and does not purport to be complete. It is subject to, and qualified in its entirety by reference to, the applicable provisions of the DGCL and our amended and restated certificate of incorporation (our "Certificate of Incorporation"), and our amended and restated bylaws (our "Bylaws"), each of which is incorporated by reference as an exhibit to the Annual Report on Form 10-K of which this Exhibit 4.13 is a part. We encourage you to read our Certificate of Incorporation, our Bylaws, and the applicable provisions of the DGCL for additional information.

**DESCRIPTION OF COMMON STOCK**

Our Certificate of Incorporation provides the authority to issue 150,000,000 shares of common stock, par value \$0.0001 per share. As December 31, 2019, there were 36,933,217 shares of common stock outstanding. Each share of our common stock has the same relative rights and is identical in all respects to each other share of our common stock. The rights, preferences and privileges of holders of our common stock are subject to the rights, preferences and privileges of the holders of shares of any series of preferred stock that we have issued or may issue in the future.

**Voting Rights**

The holders of our common stock are entitled to one vote per share on any matter to be voted upon by our stockholders. Our Certificate of Incorporation does not permit cumulative voting in connection with the election of directors.

**Dividends**

The holders of our common stock are entitled to dividends, if any, as our board of directors may declare from time to time from funds legally available for that purpose, subject to the holders of other classes of stock, if any, at the time outstanding having prior rights as to dividends, if any.

**Liquidation Rights**

Upon any voluntary or involuntary liquidation, dissolution, or winding up of our affairs, the holders of our common stock are entitled to share ratably in all assets remaining after the payment of creditors, subject to any prior liquidation distribution rights of holders of other classes of stock, if any, at the time outstanding.

**Miscellaneous**

Holders of our common stock have no preemptive, conversion, redemption or sinking fund rights. The outstanding shares of our common stock are, and the shares of common stock to be offered hereby when issued will be, validly issued, fully paid and non-assessable.

**Nasdaq Listing**

Our common stock is listed on the Nasdaq Global Market under the symbol "AXSM."

**Transfer Agent and Registrar**

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC.

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## DESCRIPTION OF PREFERRED STOCK

Our Certificate of Incorporation authorizes the issuance of up to 10,000,000 shares of preferred stock, par value \$0.0001 per share, none of which are issued and outstanding as of the date of this prospectus. We may issue, from time to time in one or more series, the terms of which may be determined at the time of issuance by our board of directors, without further action by our stockholders, shares of preferred stock and such shares may include voting rights, preferences as to dividends and liquidation, conversion rights, redemption rights and sinking fund provisions. The shares of each series of preferred stock shall have preferences, limitations and relative rights, including voting rights, identical with those of other shares of the same series and, except to the extent provided in the description of such series, of those of other series of preferred stock.

The issuance of any preferred stock could adversely affect the rights of the holders of common stock and, therefore, reduce the value of the common stock. The ability of our board of directors to issue preferred stock could discourage, delay or prevent a takeover or change in control.

The description of the terms of a particular series of preferred stock in the applicable prospectus supplement will not be complete. You should refer to the applicable certificate of designation for complete information regarding a series of preferred stock. The prospectus supplement will also contain a description of U.S. federal income tax consequences relating to the preferred stock, if material.

The terms of any particular series of preferred stock will be described in the prospectus supplement relating to that particular series of preferred stock, including, where applicable:

- the series designation, stated value and liquidation preference of such preferred stock and the number of shares offered;
- the offering price;
- the dividend rate or rates (or method of calculation), the date or dates from which dividends shall accrue, and whether such dividends shall be cumulative or noncumulative and, if cumulative, the dates from which dividends shall commence to cumulate;
- any redemption or sinking fund provisions;
- the amount that shares of such series shall be entitled to receive in the event of our liquidation, dissolution or winding-up;
- the terms and conditions, if any, on which shares of such series shall be convertible or exchangeable for shares of our stock of any other class or classes, or other series of the same class;
- the voting rights, if any, of shares of such series in addition to those set forth under the caption entitled, "Voting Rights" below;
- the status as to reissuance or sale of shares of such series redeemed, purchased or otherwise reacquired, or surrendered to us on conversion or exchange;
- the conditions and restrictions, if any, on the payment of dividends or on the making of other distributions on, or the purchase, redemption or other acquisition by us, of our common stock or of any other class of our stock ranking junior to the shares of such series as to dividends or upon liquidation (including, but not limited to, at such times as there are arrearages in the payment of dividends or sinking fund installments);
- the conditions and restrictions, if any, on the creation of Company indebtedness, or on the issue of any additional stock ranking on a parity with or prior to the shares of such series as to dividends or upon liquidation; and
- any additional dividend, liquidation, redemption, sinking or retirement fund and other rights, preferences, privileges, limitations and restrictions of such preferred stock.

### **Voting Rights**

The General Corporation Law of Delaware, or the DGCL provides that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of that preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

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## **Transfer Agent and Registrar**

The transfer agent and registrar for any series of preferred stock will be set forth in the applicable prospectus supplement.

## **Other**

Our issuance of preferred stock could decrease the amount of earnings and assets available for distribution to the holders of common stock or could adversely affect the rights and powers, including voting rights, of the holders of common stock. The issuance of preferred stock could have the effect of decreasing the market price of our common stock.

### ***Delaware Law and Certain Certificate of Incorporation and Bylaws Provisions***

Our Certificate of Incorporation and Bylaws contain provisions that could delay or prevent a change of control of our company or changes in our board of directors that our stockholders might consider favorable. Some of these provisions:

- Authorize the issuance of preferred stock which can be created and issued by the board of directors without prior stockholder approval, with rights senior to those of our common stock;
- Provide for a classified board of directors, with each director serving a staggered three-year term;
- Prohibit our stockholders from filling board vacancies, calling special stockholder meetings or taking action by written consent;
- Provide for the removal of a director only with cause and by the affirmative vote of the holders of 66 2/3 % or more of the shares then entitled to vote at an election of our directors;
- Require advance written notice of stockholder proposals and director nominations; and
- Require any action instituted against our officers or directors in connection with their service to us to be brought in the state of Delaware.

In addition, we are subject to the provisions of Section 203 of the DGCL, which may prohibit certain business combinations with stockholders owning 15% or more of our outstanding voting stock. These and other provisions in our Certificate of Incorporation, Bylaws and the DGCL could make it more difficult for stockholders or potential acquirors to obtain control of our board of directors or initiate actions that are opposed by our then-current board of directors, including a merger, tender offer or proxy contest involving our company. This provision could have the effect of delaying or preventing a change of control, whether or not it is desired by or beneficial to our stockholders. Any delay or prevention of a change of control transaction or changes in our board of directors could cause the market price of our common stock to decline.

Further, our Certificate of Incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware shall be the sole and exclusive forum for (1) any derivative action or proceeding brought on behalf of our company, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or agents to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the DGCL, or (4) any action asserting a claim governed by the internal affairs doctrine, in each such case subject to such Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein.

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 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 or agents, which may discourage such lawsuits against us and our directors, officers, employees and agents. Further, this choice of forum provision does not preclude or contract the scope of exclusive federal or concurrent jurisdiction for any actions brought under the Securities Act of 1933, as amended (the "Securities Act") or the Exchange Act. Section 27 of the Exchange Act creates exclusive federal jurisdiction over all suits brought to enforce any duty or liability created by the Exchange

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Act or the rules and regulations thereunder. As a result, the exclusive forum provision will not apply to suits brought to enforce any duty or liability created by the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction. In addition, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all suits brought to enforce any duty or liability created by the Securities Act or the rules and regulations thereunder. As a result, the exclusive forum provision will not apply to suits brought to enforce any duty or liability created by the Securities Act or any other claim for which the federal and state courts have concurrent jurisdiction. Accordingly, our exclusive forum provision will not relieve us of our duties to comply with the federal securities laws and the rules and regulations thereunder, and our stockholders will not be deemed to have waived our compliance with these laws, rules and regulations.

### **Indemnification**

Our Certificate of Incorporation contains provisions permitted under the DGCL relating to the liability of directors. The provisions eliminate, to the extent legally permissible, a director's liability for monetary damages for a breach of fiduciary duty, except in circumstances involving wrongful acts, such as the breach of a director's duty of loyalty or acts or omissions that involve intentional misconduct or a knowing violation of law. The limitation of liability described above does not alter the liability of our directors and officers under federal securities laws. Furthermore, our certificate of incorporation contains provisions to indemnify our directors and officers to the fullest extent permitted by the DGCL. These provisions do not limit or eliminate our right or the right of any stockholder of ours to seek non-monetary relief, such as an injunction or rescission in the event of a breach by a director or an officer of his duty of care to us. We believe that these provisions assist us in attracting and retaining qualified individuals to serve as directors.

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Portions of this Exhibit have been redacted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed. Information that was omitted has been noted in this document with a placeholder identified by the mark "[\*\*\*]".

## LICENSE AGREEMENT

THIS LICENSE AGREEMENT (this "AGREEMENT") is made effective as of the 10th of January 2020 (the "EFFECTIVE DATE"), by and among Axsome Therapeutics, Inc., a corporation organized and existing under the laws of Delaware with offices at 200 Broadway, 3rd Floor, New York, NY 10038 ("AXSOME") and Pfizer Inc., a corporation organized and existing under the laws of Delaware with offices at 235 East 42<sup>nd</sup> Street, New York, NY 10017 ("PFIZER"). AXSOME and PFIZER may, from time-to-time, be individually referred to as a "PARTY" and collectively referred to as the "PARTIES".

WHEREAS, AXSOME wishes to receive and PFIZER wishes to grant certain licenses to certain rights to intellectual property related to the compound reboxetine and its enantiomeric form, esreboxetine on the terms and conditions set forth herein; and

NOW, THEREFORE, in consideration of the mutual agreements and covenants set forth herein and other good and valuable consideration, the receipt and sufficiency of which the PARTIES hereby acknowledge, the PARTIES hereby agree as follows:

1. Definitions; Interpretation. Except where the context expressly requires otherwise, (a) the use of any gender herein shall be deemed to encompass references to either or both genders, and the use of the singular shall be deemed to include the plural (and vice versa), (b) the words "include", "includes" and "including" shall be deemed to be followed by the phrase "without limitation", (c) the word "will" shall be construed to have the same meaning and effect as the word "shall", (d) any definition of or reference to any agreement, instrument or other document herein shall be construed as referring to such agreement, instrument or other document as from time to time amended, supplemented or otherwise modified (subject to any restrictions on such amendments, supplements or modifications set forth herein), (e) any reference herein to any PERSON shall be construed to include the PERSON's successors and assigns, (f) the words "herein", "hereof" and "hereunder", and words of similar import, shall be construed to refer to this AGREEMENT in its entirety and not to any particular provision hereof, (g) all references herein to Sections, Exhibits or Schedules shall be construed to refer to Sections, Exhibits or Schedules of this AGREEMENT, and references to this AGREEMENT include all Exhibits and Schedules hereto, (h) the word "notice" means notice in writing (whether or not specifically stated) and shall include notices, consents, approvals and other written communications contemplated under this AGREEMENT, (i) provisions that require that a PARTIES, the PARTIES or any committee hereunder "agree", "consent" or "approve" or the like shall require that such agreement, consent or approval be specific and in writing, whether by written agreement, letter, approved minutes or otherwise (but excluding e-mail and instant

messaging), (j) references to any specific law, rule or regulation, or article, section or other division thereof, shall be deemed to include the then-current amendments thereto or any replacement or successor law, rule or regulation thereof and (k) the term "or" shall be interpreted in the inclusive sense commonly associated with the term "and/or". The following definitions shall have the meanings set forth below:

1.1 "AFFILIATE" means, with respect to a PARTY, any PERSON that controls, is controlled by, or is under common control with that PARTY. For the purpose of this definition only, "control" shall mean: (a) the possession, directly or indirectly, of the power to direct or cause the direction of the management or policies of an entity, whether through the ownership of voting securities or other ownership interest, by contract or otherwise, or (b) the ownership, directly or indirectly, of fifty percent (50%) or more of the voting securities or other ownership interest of such entity.

1.2 "AGREEMENT" has the meaning set forth in the PREAMBLE.

1.3 "API" means an active pharmaceutical ingredient.

1.4 "APPLICABLE LAW" means any applicable law, statute, rule, regulation, order, judgment or ordinance of, if applicable, any GOVERNMENTAL AUTHORITY.

1.5 "AXSOME INDEMNITEES" has the meaning set forth in Section 12.2.

1.6 "BANKRUPTCY CODE" means the United States Bankruptcy Code, as amended or under any similar laws or statutes of the United States or any state thereof.

1.7 "BANKRUPTCY EVENT" means the occurrence of any of the following: (a) the institution of any bankruptcy, receivership, insolvency, reorganization or other similar proceedings by or against a PARTY under any bankruptcy, insolvency, or other similar law now or hereinafter in effect, including any section or chapter of the BANKRUPTCY CODE, where in the case of involuntary proceedings such proceedings have not been dismissed or discharged within ninety (90) days after they are instituted, (b) the insolvency or making of an assignment for the benefit of creditors or the admittance by a PARTY of any involuntary debts as they mature, (c) the institution of any reorganization, arrangement or other readjustment of debt plan of a PARTY not involving the BANKRUPTCY CODE, (d) appointment of a receiver for all or substantially all of a PARTY's assets, or (e) any

corporate action taken by the board of directors of a PARTY in furtherance of any of the foregoing actions.

1.8 “BUSINESS DAY” means any day other than a Saturday, a Sunday or a day on which commercial banks located in New York, New York are authorized or required by APPLICABLE LAW to remain closed.

1.9 “CALENDAR QUARTER” means any of the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 and December 31.

1.10 “CALENDAR YEAR” means each calendar year from the first day of the month of January until the last day of the month of December.

1.11 “CAP” has the meaning set forth in Section 13.2.

1.12 “CDA” has the meaning set forth in Section 18.11.

1.13 “CLAIM” means any demand, claim, action or proceeding (whether criminal or civil, in contract, tort or otherwise) for losses, damages (including for consequential damages, lost profits or punitive damages), liabilities, costs and expenses (including for attorneys’ fees).

1.14 “CLINICAL TRIAL” means a human clinical study conducted on human subjects that is designed to (a) investigate whether or establish that a pharmaceutical product is reasonably safe for continued testing, (b) investigate the safety and efficacy of the pharmaceutical product for its intended use, and to define warnings, precautions and adverse reactions that may be associated with the pharmaceutical product in the dosage range to be prescribed or (c) support REGULATORY APPROVAL of such pharmaceutical product or label expansion of such pharmaceutical product. Without limiting the foregoing, CLINICAL TRIAL includes phase 1, phase 2 and phase 3 clinical investigations as such terms are defined in Section 312.21 of Title 21 of the Code of Federal Regulations in the United States of America.

1.15 “COMBINATION PRODUCT” means a PRODUCT that contains a COMPOUND and at least one other NON-COMPOUND API.

1.16 “COMMERCIALIZE” means with respect to subject matter that is a COMPOUND or a PRODUCT, to market, promote, distribute, offer for sale, sell or otherwise commercialize such subject matter. COMMERCIALIZED and COMMERCIALIZATION has the corresponding meaning.

1.17 “COMMERCIALLY REASONABLE EFFORTS” means, with respect to the efforts and resources to be expended by a PARTY and with respect to any objective, those reasonable, good faith efforts and resources expended to accomplish such objective, including relating to the DEVELOPMENT, MANUFACTURING or COMMERCIALIZATION of a COMPOUND or PRODUCT, as commonly dedicated by a company of similar size and resources in the research-based pharmaceutical industry in performing applicable activities with respect to a product of similar commercial potential at a similar stage in its lifecycle, in each case taking into account issues of safety and efficacy, product profile, the proprietary position, the then-current competitive environment for such product and the likely timing of such product’s entry into the market,

the regulatory environment and the status of such product, profitability (including pricing and reimbursement) and other relevant scientific, technical, regulatory and commercial factors.

1.18 “COMPOUND” means reboxetine and or esreboxetine and any salt, solvate, hydrate, stereoisomer, prodrug, metabolite, isomer, enantiomer, tautomer or polymorph of any of the foregoing compounds described in clauses (a), (b) or (c).

1.19 “CONFIDENTIAL INFORMATION” has the meaning set forth in Section 9.1.

1.20 “CONTROL” means, with respect to any INTELLECTUAL PROPERTY RIGHTS or other rights to provide data or other information, the legal authority or right (whether by ownership, license or otherwise) of a PARTY to grant a license or a sublicense of or under such INTELLECTUAL PROPERTY RIGHTS to the other PARTY or provide such data or other information to such other PARTY as set forth in this AGREEMENT without breaching the terms of any agreement with a THIRD PARTY. “CONTROLLED” and “CONTROLLING” have the corresponding meanings.

1.21 “DEVELOP” means with respect to subject matter that is a COMPOUND or a PRODUCT, to conduct any and all research and development activities necessary to obtain REGULATORY APPROVAL of such subject matter. “DEVELOPED”, “DEVELOPING” and DEVELOPMENT have corresponding meanings.

1.22 “DISPUTE” has the meaning set forth in Section 17.1.

1.23 “EFFECTIVE DATE” has the meaning set forth in the PREAMBLE.

1.24 “ELECTION NOTICE” has the meaning set forth in Section 8.3.7.

1.25 “EXPLOIT” means with respect to subject matter that is a COMPOUND or a PRODUCT, any one or more of the following: to DEVELOP, to MANUFACTURE, to use, to COMMERCIALIZE or to otherwise to exploit the subject matter. “EXPLOITATION”, “EXPLOITING” and “EXPLOITED” has the corresponding meaning.

1.26 “FDA” means the United States Food and Drug Administration, or a successor federal agency thereto.

1.27 “FIELD” means the treatment, diagnosis or prevention of any disease or condition in humans.

1.28 “FIRST COMMERCIAL SALE” means, with respect to a PRODUCT, the first sale of such PRODUCT to a THIRD PARTY by AXSOME, AXSOME’s AFFILIATE or a PRODUCT TRANSFEREE in the TERRITORY.

1.29 “FORCE MAJEURE EVENT” has the meaning set forth in Section 18.4.

1.30 “GAAP” means United States generally accepted accounting principles, consistently applied.

1.31 “GENERIC COMPETITION” means, with respect to a PRODUCT, the condition in which the aggregate market share in the TERRITORY during a CALENDAR QUARTER of a GENERIC PRODUCT is [\*\*\*] percent ([\*\*\*]%) or more by unit volume (based on data provided by a reliable THIRD PARTY data source mutually agreed to by

the PARTIES) of combined unit sales of the PRODUCT and all applicable GENERIC PRODUCTS.

1.32 “GENERIC PRODUCT” means, with respect to a PRODUCT, any pharmaceutical product that (a) is sold by a THIRD PARTY in the TERRITORY without the prior authorization of AXSOME, an AFFILIATE of AXSOME or a PRODUCT TRANSFEREE, (b) receives approval, registration, license or authorization to sell such product in the TERRITORY in full or partial reliance on the REGULATORY APPROVAL of the PRODUCT and (c) is determined by a REGULATORY AUTHORITY to be therapeutically equivalent to and substitutable with the PRODUCT, it being acknowledged that the foregoing standard is intended to be generally consistent with the standard set forth in the preface to the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book, as amended from time to time) published by the U.S. Food and Drug Administration. For avoidance of doubt, GENERIC PRODUCT includes a product approved under Section 505(j) of the United States Federal Food, Drug, and Cosmetic Act.

1.33 “GOVERNMENTAL AUTHORITY” means any court, agency, department, authority or other instrumentality of national, state, country, city or other political subdivision.

1.34 “INDEMNITEE” is defined in Section 12.3.

1.35 “INDEMNITOR” is defined in Section 12.3.

1.36 “INTELLECTUAL PROPERTY RIGHTS” means any and all trade secrets, copyrights, PATENT RIGHTS, trademarks, moral rights, KNOW-HOW and any and all other intellectual property or proprietary rights now known or hereafter recognized in any jurisdiction.

1.37 “KNOW-HOW” means any proprietary invention, discovery, development, data, information, process, method, technique or other know-how, whether or not patentable.

1.38 “KNOWLEDGE” means, with respect to a PARTY, the actual knowledge of the PARTY’s in-house patent counsel employed by the PARTY whose area of responsibility relates to the representation or warranty that the PARTY makes under this AGREEMENT.

1.39 “LICENSED IP” means, collectively, the LICENSED PATENT RIGHTS and LICENSED KNOW-HOW.

1.40 “LICENSED KNOW-HOW” means all KNOW-HOW that is listed in the TRANSFER SCHEDULE.

1.41 “LICENSED PATENT RIGHTS” means all PATENT RIGHTS listed in Schedule 1.40; and all PATENT RIGHTS resulting from any interference, *inter partes* review, reexamination, reissue or revival of any of the foregoing PATENT RIGHTS; and extensions or restorations of any of the foregoing, by existing or future extension or restoration mechanisms, including patent term adjustments, patent term extensions, supplementary protection certificates and the equivalent thereof.

1.42 “MANUFACTURE” means with respect to subject matter that is a COMPOUND, a PRODUCT or a component thereof, to make, produce, manufacture, process, fill, finish,

package, label, perform quality assurance testing, release, ship or store such subject matter.  
“MANUFACTURING” and “MANUFACTURED” has the corresponding meaning.

1.43 “MARGINAL ROYALTY” means for each MARGINAL SALES RANGE an amount equal to the applicable NET SALES within the MARGINAL SALES RANGE multiplied by the corresponding MARGINAL ROYALTY RATE.

1.44 “MARGINAL ROYALTY RATES” means the royalty rates set forth in Schedule 5.5 that correspond to each of the MARGINAL SALES RANGES.

1.45 “MARGINAL SALES RANGES” means for each PRODUCT the ranges as set forth in Schedule 5.5 of NET SALES in a CALENDAR YEAR of the PRODUCT that are made during the ROYALTY TERM.

1.46 “MILESTONE PAYMENTS” means, collectively, the REGULATORY APPROVAL MILESTONE PAYMENTS and the SALES MILESTONE PAYMENTS.

1.47 “NET SALES” means, with respect to a PRODUCT distributed or sold in the TERRITORY to THIRD PARTIES by AXSOME, AXSOME’s AFFILIATES or any PRODUCT TRANSFEREE, gross receipts from sales of such PRODUCTS in the TERRITORY, less in each case (a) sales returns and allowances actually paid, granted or accrued, including trade, quantity and cash discounts and other adjustments, including those granted on account of price adjustments, billing errors, rejected goods, damaged or defective goods, recalls, returns, rebates, chargebacks, reimbursements or similar payments granted or given to wholesalers, distributors, buying groups or other institutions, (b) customs or excise duties, valued-added taxes, sales taxes, consumption taxes and other taxes (except income taxes) or duties relating to sales, any payment in respect of sales to the United States government, any state government or any foreign government, or to any other governmental authority, or with respect to any government-subsidized program or managed care organization, (c) freight and insurance (to the extent that such costs are included in the amount invoiced to customers and included in gross sales) up to but not more than [\*\*\*] percent ([\*\*\*]%) of the gross receipts from sales in the TERRITORY of the applicable PRODUCTS, and (d) reasonable distributors’ and inventory management fees, including fees for services provided by wholesalers and warehousing chains, in connection with the sale and distribution of PRODUCTS. NET SALES shall be determined from AXSOME’s books and records maintained in accordance with GAAP consistently applied. NET SALES of a PRODUCT that is a COMBINATION PRODUCT shall be calculated as set forth in Schedule 1.46. For clarity, sales of a PRODUCT between any of AXSOME, an AFFILIATE of AXSOME, and a PRODUCT TRANSFEREE shall be disregarded for purposes of calculating NET SALES. Any sale made for academic research or clinical purposes or for a bona fide charitable purpose at an invoice price equal

to or less than the costs of goods sold plus freight for the units sold shall not be considered a "NET SALE".

1.48 "NON-COMPOUND API" has the meaning set forth in Schedule 1.16.

1.49 "OTHER PRODUCT" has the meaning set forth in Schedule 1.16.

1.50 "PARTY" and "PARTIES" has the meaning set forth in the PREAMBLE.

1.51 "PATENT MAINTENANCE" has the meaning set forth in Section 8.3.

1.52 "PATENT PROSECUTION" has the meaning set forth in Section 8.3.

1.53 "PATENT RIGHTS" means any and all (a) issued patents, (b) pending patent applications, including all provisional applications, divisions, continuations, substitutions, continuations-in-part and renewals, and all patents granted thereon, (c) patents-of-addition, re-examinations, reissues and extensions or restorations by existing or future extension or restoration mechanisms, including patent term adjustments, patent term extensions, supplementary protection certificates or the equivalent thereof, (d) inventor's certificates, (e) other forms of government-issued rights substantially similar to any of the foregoing and (f) United States and foreign counterparts of any of the foregoing.

1.54 "PERSON" means an individual, corporation, partnership, limited liability company, trust, business trust, association, joint stock company, joint venture, pool, syndicate, sole proprietorship, unincorporated organization, governmental authority or any other form of entity not specifically listed herein.

1.55 "PFIZER INDEMNITEES" has the meaning set forth in Section 12.1.

1.56 "PREAMBLE" means the first full paragraph of this AGREEMENT.

1.57 "PRODUCT" means a pharmaceutical product that contains or incorporates one or more COMPOUNDS, and which may also contain or incorporate one or more NON-COMPOUND APIs.

1.58 "PRODUCT TRANSFEREE" means with respect to a PRODUCT a THIRD PARTY that either: (a) directly receives from AXSOME or an AFFILIATE of AXSOME

rights to COMMERCIALIZE the PRODUCT; or (b) receives from another PRODUCT TRANSFEREE rights to COMMERCIALIZE the PRODUCT.

1.59 “RECIPIENTS” has the meaning set forth in Section 9.2.

1.60 “REGULATORY APPROVAL” means, with respect to a PRODUCT, any approval, registration, license or authorization that is necessary to COMMERCIALIZE such PRODUCT in the TERRITORY.

1.61 “REGULATORY APPROVAL MILESTONES” means the milestones set forth in Schedule 5.3.

1.62 “REGULATORY APPROVAL MILESTONE PAYMENTS” means the payments set forth in Schedule 5.3 that correspond to each of the REGULATORY APPROVAL MILESTONES.

1.63 “REGULATORY AUTHORITY” means any GOVERNMENTAL AUTHORITY responsible for granting a REGULATORY APPROVAL.

1.64 “REGULATORY FILING” means, with respect to a PRODUCT, any submission to a REGULATORY AUTHORITY of any appropriate application related to REGULATORY APPROVAL, including, without limitation, any an investigational new drug application, new drug application, submission to a regulatory advisory board, marketing authorization application and any supplement or amendment thereto.

1.65 “RELEVANT RECORDS” has the meaning set forth in in Section 7.1.

1.66 “RESIDUALS” means, with respect to a PARTY, information in non-tangible form which is retained in the unaided memory of individuals employed or retained by such PARTY including ideas, concepts, know-how or techniques contained therein.

1.67 “REVIEW PERIOD” has the meaning set forth in Section 15.3.

1.68 “ROFN” has the meaning set forth in Section 10.2.

1.69 “ROFN EXERCISE NOTICE” has the meaning set forth in Section 10.4.

1.70 “ROFN MILESTONE” means, with respect to a PRODUCT, the occurrence of any of the following: (a) [\*\*\*]; (b) [\*\*\*]; (c) receipt by AXSOME, its AFFILIATE or SUBLICENESEE (if applicable) of top-line data from a [\*\*\*] of the [\*\*\*]; or (d) [\*\*\*].

1.71 “ROFN NEGOTIATION PERIOD” has the meaning set forth in Section 10.1.

1.72 “ROFN NOTICE PERIOD” has the meaning set forth in Section 10.1.

1.73 “ROFN OFFER NOTICE” has the meaning set forth in Section 10.3.

1.74 “ROYALTY PAYMENTS” means for each PRODUCT and for each CALENDAR YEAR, the sum of MARGINAL ROYALTIES paid in accordance with Section 5.5.

1.75 “ROYALTY TERM” means, with respect to each PRODUCT the period commencing on the FIRST COMMERCIAL SALE of such PRODUCT and expiring upon the later of: (a) [\*\*\*] following the date of FIRST COMMERCIAL SALE of the PRODUCT, (b) the expiration of all regulatory or data exclusivity for such PRODUCT in the TERRITORY or (c) the date upon which the manufacture, use or sale of such PRODUCT in such country would no longer infringe, but for the license granted herein, a



VALID CLAIM of a LICENSED PATENT RIGHT covering such PRODUCT in the TERRITORY.

- 1.76 “SALES MILESTONES” means the milestones set forth in Schedule 5.4.
- 1.77 “SALES MILESTONE PAYMENTS” means the payments set forth in Schedule 5.4 that correspond to each of the SALES MILESTONES.
- 1.78 “SHARES” has the meaning set forth in Section 5.1.
- 1.79 “SHARE TRANSFER” has the meaning set forth in Section 5.1.
- 1.80 “SHARE TRANSFER AGREEMENT” means an agreement having the terms, conditions and covenants set forth in Schedule 1.79.
- 1.81 “SHARE TRANSFER DATE” means the date which is the earlier of: (a) the Date of the SHARE TRANSFER AGREEMENT; and (b) the date upon which the SHARE TRANSFER occurs.
- 1.82 “SIGNIFICANT TRANSACTION” means with respect to a PRODUCT [\*\*\*].
- 1.83 “SIGNIFICANT TRANSACTION PAYMENT” has the meaning set forth in Section 5.6.
- 1.84 “SIGNIFICANT TRANSACTION VALUE” means all compensation received by AXSOME other than reimbursement of costs and expenses incurred by AXSOME, including but not limited to patent costs, withholding taxes and other amounts actually withheld from or deducted against the amounts paid to AXSOME.
- 1.85 “SUBLICENSE” has the meaning set forth in Section 2.2.
- 1.86 “SUBLICENSEE” means a THIRD PARTY that has been granted a SUBLICENSE pursuant to Section 2.2.
- 1.87 “TAX ACTION” has the meaning set forth in Section 6.9.2.
- 1.88 “TERM” has the meaning set forth in Section 14.1.
- 1.89 “TERRITORY” means the territory of the United States of America.
- 1.90 “THIRD PARTY” means any PERSON other than a PARTY or an AFFILIATE of a PARTY.
- 1.91 “THIRD PARTY INFRINGEMENT” has the meaning set forth in Section 8.4.1.
- 1.92 “THIRD PARTY ROYALTIES” means with respect to a PRODUCT any royalties on the NET SALES of the PRODUCT that are NECESSARY to be paid for a license that is granted under a PATENT RIGHT of a THIRD PARTY. “NECESSARY” as used in this Section 1.91 means with respect to a PATENT RIGHT, that the PATENT RIGHT would be infringed, if not for the grant of such license, by activity that has actually occurred in

the DEVELOPMENT, MANUFACTURE or COMMERCIALIZATION of the PRODUCT.

1.93 “TRANSFER SCHEDULE” means the schedule of documents set forth in Schedule 1.92 relating to the LICENSED KNOW-HOW.

1.94 “UPFRONT PAYMENT” has the meaning set forth in Section 5.2.

1.95 “VALID CLAIM” means with respect to a particular country, a claim of a PATENT RIGHT within the LICENSED PATENT RIGHTS that: (a) with respect to an issued and unexpired patent, (i) has not been held permanently revoked, unenforceable or invalid by a decision of a court or other governmental authority of competent jurisdiction, which decision is unappealed or unappealable within the time allowed for appeal and (ii) has not expired or been cancelled, withdrawn, abandoned, disclaimed or admitted to be invalid or unenforceable through reissue, disclaimer or otherwise and (b) with respect to a pending patent application, has been prosecuted in good faith, has not been abandoned or finally disallowed without the possibility of appeal or refiling of such application.

1.96 “VAT” has the meaning set forth in Section 6.9.1.

## 2. License Grant

2.1 Subject to the terms and conditions of this AGREEMENT, PFIZER hereby grants to AXSOME an exclusive (even as to PFIZER), sublicensable (subject to Section 2.2), royalty-bearing right and license under the LICENSED IP to EXPLOIT the COMPOUNDS and the PRODUCTS in the FIELD within the TERRITORY.

2.2 Sublicense Rights. Subject to the provisions of Section 2.2.1, AXSOME shall be entitled to sublicense the rights granted to it by PFIZER under this AGREEMENT to: (a) an AFFILIATE of AXSOME; (b) THIRD PARTIES; and (c) pursuant to an applicable SIGNIFICANT TRANSACTION provided that all of the provisions of Section 10 relating to the ROFNs have been complied with, (each such sublicense, a “SUBLICENSE”).

Notwithstanding the foregoing, the requirements set forth in Subsection 2.2.1 and 2.2.3 do not apply to SUBLICENSES granted by AXSOME to THIRD PARTIES to the extent necessary for conducting DEVELOPMENT or MANUFACTURING activities on behalf of AXSOME pursuant to this AGREEMENT only (e.g., contract manufacturing organizations, clinical research organizations).

2.2.1 All SUBLICENSES granted to THIRD PARTIES (except for those granted for purposes of DEVELOPMENT or MANUFACTURING on behalf of AXSOME or an AFFILIATE of AXSOME) shall: (a) be in writing duly executed by AXSOME and the applicable THIRD PARTY; (b) not include any term, condition or covenant that is inconsistent or contrary to those set forth in this AGREEMENT; (c) include PFIZER as a third party beneficiary with the right to enforce the terms, conditions and covenants thereunder to the extent related to PFIZER’s rights granted under this AGREEMENT; (d) prohibit the SUBLICENSEE from granting further SUBLICENSES; (e) not include any term, condition or provision that restricts or adversely impacts the ROFN; and (f) include provisions consistent with Section 14.5.2.

2.2.2 In no event shall any SUBLICENSE relieve AXSOME of any of its obligations under this AGREEMENT.

2.2.3 AXSOME shall furnish to PFIZER a true and complete copy of each SUBLICENSE granted to THIRD PARTIES (except for those granted for purposes of DEVELOPMENT or MANUFACTURING on behalf of AXSOME or an AFFILIATE of AXSOME) and each amendment thereto, within thirty (30) days after such SUBLICENSE or amendment having been executed; provided that AXSOME may redact any terms not necessary to confirm compliance with the terms of this AGREEMENT.

2.3 Retained Rights. AXSOME acknowledges and agrees that PFIZER shall retain the following rights under the LICENSED IP: (a) to conduct (or have conducted) directly or by contractors or collaborators in the TERRITORY any research and development activities solely on behalf of PFIZER or its AFFILIATES solely for use outside the Territory; (b) to supply in the TERRITORY through [\*\*\*] small quantities of the COMPOUNDS to suppliers of research reagents solely as research reagents; (c) to supply small quantities of the COMPOUNDS to THIRD PARTIES in the TERRITORY for academic, educational or other non-commercial research purposes (provided no such use of the COMPOUNDS is for human or veterinary clinical purposes); and (d) to MANUFACTURE or have MANUFACTURED the COMPOUNDS and PRODUCTS in the TERRITORY, but solely for the purposes of MANUFACTURING, DEVELOPMENT, COMMERCIALIZATION or other EXPLOITATION (or having MANUFACTURED, DEVELOPED, COMMERCIALIZED or otherwise EXPLOITED) outside of the TERRITORY. For clarity, no provision of this AGREEMENT shall be deemed to restrict either PARTY's rights to perform activities permitted under APPLICABLE LAW of the TERRITORY related to safe harbor, research exemptions, executive declarations of urgent public health needs or the like (e.g., exemptions under 35 USC 271(e)(1)).

2.4 Residuals. PFIZER shall be permitted to use for any purpose the RESIDUALS resulting from its access to or work with any COMPOUND, PRODUCT or LICENSED IP.

2.5 No Additional Rights. Nothing in this AGREEMENT shall be construed to confer any rights upon AXSOME or PFIZER by implication, estoppel, or otherwise as to any technology or INTELLECTUAL PROPERTY RIGHTS of the other PARTY or its AFFILIATES other than the rights in LICENSED IP expressly granted herein, regardless of whether such technology or INTELLECTUAL PROPERTY RIGHTS shall be dominant or subordinate to any LICENSED IP.

3. Transfer of Know-How. Within thirty (30) days of the EFFECTIVE DATE, PFIZER shall transfer to AXSOME the documentation and materials set forth in the TRANSFER SCHEDULE.

4. Development; Manufacturing; Commercialization

4.1 Sole Responsibility, Authority and Control. As between the PARTIES and subject to the provisions of Section 2.3 (retained rights), AXSOME shall have sole responsibility for the cost and expenses of, and the sole authority over and control of the DEVELOPMENT, MANUFACTURE, seeking and maintaining REGULATORY

APPROVALS and COMMERCIALIZATION of COMPOUNDS and PRODUCTS in the TERRITORY for the FIELD.

4.2 Diligence. AXSOME shall use COMMERCIALY REASONABLE EFFORTS and, if applicable, shall ensure that its AFFILIATES and SUBLICENSEES use COMMERCIALY REASONABLE EFFORTS to DEVELOP, MANUFACTURE, seek and maintain REGULATORY APPROVALS and COMMERCIALIZE the COMPOUNDS and PRODUCTS in the TERRITORY for the FIELD.

4.3 Progress Reporting. At least ninety (90) days prior to the start of each CALENDAR YEAR, AXSOME shall provide to PFIZER a report including (a) an update on the progress of AXSOME's DEVELOPMENT and COMMERCIALIZATION activities, including studies completed or in progress, studies planned, and key achievements to date in the CALENDAR YEAR, (b) a summary of the planned DEVELOPMENT and COMMERCIALIZATION activities for the upcoming CALENDAR YEAR, including studies completed or in progress, studies planned, and key achievements and milestones that are expected and (c) a non-binding three (3) year forecast of payments that are anticipated to be made to PFIZER pursuant to Section 5, on a CALENDAR QUARTER basis for the first year and on a CALENDAR YEAR basis for the second and third years, provided however that AXSOME shall not be required to provide a forecast of ROYALTY PAYMENTS until after the first report of ROYALTY PAYMENT pursuant to Section 5.5.4 is provided to PFIZER. With respect to the foregoing, AXSOME shall be obligated to use no more than COMMERCIALY REASONABLE EFFORTS to provide the key achievements and milestones that are expected and the non-binding forecast of payments under Subsection (c) of this Section 4.3. AXSOME would make available on a quarterly basis for a reasonable period of time, knowledgeable personnel to respond to questions from PFIZER or its AFFILIATES pertaining to the development and commercialization of the PRODUCT in order to assist PFIZER or its AFFILIATES with fulfilling any of PFIZER's or its AFFILIATES revenue recognition procedures as they pertain to payments owed or potentially owed to PFIZER under this AGREEMENT.

5. Consideration

5.1 Equity. In consideration of the licenses and rights granted to AXSOME hereunder, AXSOME shall on the SHARE TRANSFER DATE issue to PFIZER, that number of shares of AXSOME's common stock (the "SHARES") having a value in the amount set forth in Schedule 5.1 based on the average closing price of the AXSOME's common stock on the U.S. public market or exchange in which AXSOME shares are listed or traded for the ten (10) consecutive trading days immediately preceding the date of this AGREEMENT (the "SHARE TRANSFER"). On the EFFECTIVE DATE the PARTIES shall enter into the SHARE TRANSFER AGREEMENT setting forth the terms and conditions of the SHARE TRANSFER, which shall include a restriction on the sale by PFIZER of the SHARES prior to the first anniversary of the EFFECTIVE DATE.

Upfront Payment.

5.2.1 As additional consideration of the licenses and rights granted to AXSOME hereunder, AXSOME shall pay to PFIZER a one-time, upfront, non-refundable and

non-creditable payment in the amount set forth in Schedule 5.2 (the “UPFRONT PAYMENT”).

5.2.2 The UPFRONT PAYMENT shall be paid as set forth in Section 6.1.

5.3 Regulatory Approval Milestone Payments

5.3.1 As additional consideration of the licenses and rights granted to AXSOME hereunder, AXSOME shall pay to PFIZER the REGULATORY APPROVAL MILESTONE PAYMENTS after achievement of the corresponding REGULATORY APPROVAL MILESTONE set forth in Schedule 5.3 is achieved.

5.3.2 The REGULATORY APPROVAL MILESTONE PAYMENTS shall be paid as set forth in Section 6.2.

5.4 Sales Milestone Payments. As additional consideration of the licenses and rights granted to AXSOME hereunder, AXSOME shall pay to PFIZER the SALES MILESTONE PAYMENTS set forth in Schedule 5.4 as follows:

5.4.1 SALES MILESTONE PAYMENTS shall be paid after achievement of the corresponding SALES MILESTONES 1 to 3;

5.4.2 On or after [\*\*\*] from the FIRST COMMERCIAL SALE of any PRODUCT and after SALES MILESTONE 4 has been achieved, AXSOME shall pay PFIZER the SALES MILESTONE PAYMENT that corresponds to SALES MILESTONE 4, provided that: (a) the SALES MILESTONE PAYMENT corresponding to SALES MILESTONE 1 has not yet been paid; and (b) upon the subsequent achievement of SALES MILESTONE 1, the SALES MILESTONE PAYMENT that corresponds to SALES MILESTONE 1 shall be reduced by the amount paid for SALES MILESTONE 4;

5.4.3 For clarity, in the event that more than one SALES MILESTONE is attained in a CALENDAR YEAR, all applicable SALES MILESTONE PAYMENTS shall be paid for the applicable CALENDAR YEAR; and

5.4.4 The SALES MILESTONE PAYMENTS shall be paid as set forth in Section 6.3.

5.5 Royalty Payments

5.5.1 Generally. As additional consideration of the licenses and rights granted to AXSOME hereunder, AXSOME shall pay to PFIZER for each PRODUCT the ROYALTY PAYMENTS based on the corresponding MARGINAL ROYALTIES calculated on a CALENDAR QUARTER basis beginning in the CALENDAR QUARTER of the FIRST COMMERCIAL SALE of the PRODUCT until termination of the ROYALTY TERM for such PRODUCT, subject to any applicable adjustments as set forth in Section 5.5.3.

5.5.2 Timing of Payments. The ROYALTY PAYMENTS shall be paid as set forth in Section 6.4.

5.5.3 Adjustments

(a) For each PRODUCT, AXSOME shall be entitled to reduce the ROYALTY PAYMENTS by [\*\*\*] percent ([\*\*\*]%) of any THIRD PARTY ROYALTIES actually paid to a THIRD PARTY for the NET SALES corresponding to the ROYALTY PAYMENTS, provided that such reduction shall be no more than that which reduces the ROYALTY PAYMENT for the applicable NET SALES to [\*\*\*]percent ([\*\*\*]

(b) For each PRODUCT, AXSOME shall be entitled to reduce the ROYALTY PAYMENTS by [\*\*\*] percent ([\*\*\*]%) for any CALENDAR QUARTER in which GENERIC COMPETITION exists in the TERRITORY, provided that such reduction shall be no more than that which reduces the ROYALTY PAYMENT for the applicable NET SALES to [\*\*\*] percent ([\*\*\*]).

(c) The total reduction of ROYALTY PAYMENTS pursuant to Subsections (a) and (b) of this Section 5.5.3 shall be no more than that which reduces the ROYALTY PAYMENT for the applicable NET SALES to [\*\*\*] percent ([\*\*\*]). Notwithstanding the foregoing, if the reduction of ROYALTY PAYMENTS pursuant to Subsections (a) and (b) of this Section 5.5.3 would result in a ROYALTY PAYMENT for the applicable NET SALES of less than [\*\*\*] percent ([\*\*\*]), the amount of the excess shall be carried forward and treated as a royalty reduction under this Section 5.5.3 in the following CALENDAR QUARTERS until all such amounts are deducted.

5.5.4 Reporting. On or before [\*\*\*] ([\*\*\*]) days after each CALENDAR QUARTER of the ROYALTY TERM, AXSOME shall provide PFIZER with a report for each applicable PRODUCT that includes detailed information regarding applicable NET SALES calculations (including any deductions that may be applicable) and applicable ROYALTY PAYMENTS calculations. All reports shall be the CONFIDENTIAL INFORMATION of AXSOME.

5.5.5 Acknowledgement. The PARTIES acknowledge that ROYALTY PAYMENTS for NET SALES made in the absence of a VALID CLAIM covering a PRODUCT are paid as partial consideration for the rights granted under this AGREEMENT that are other than PATENT RIGHTS, including rights in the LICENSED KNOW-HOW.

5.6 Significant Transaction Payment. In the event that AXSOME consummates a SIGNIFICANT TRANSACTION with a THIRD PARTY on or before [\*\*\*] ([\*\*\*]) [\*\*\*]after the EFFECTIVE DATE, AXSOME shall pay PFIZER a payment of [\*\*\*]percent ([\*\*\*]) of the SIGNIFICANT TRANSACTION VALUE actually received from such THIRD PARTY pursuant to the SIGNIFICANT TRANSACTION (the

“SIGNIFICANT TRANSACTION PAYMENT”). All SIGNIFICANT TRANSACTION PAYMENTS shall be paid in accordance with Section 6.5.

6. Payments

6.1 Upfront Payment. AXSOME shall pay to PFIZER the UPFRONT PAYMENT on the EFFECTIVE DATE.

6.2 Regulatory Approval Milestone Payments. AXSOME shall pay to PFIZER each REGULATORY APPROVAL MILESTONE PAYMENTS no later than [\*\*\*] ([\*\*\*) [\*\*\*] following the occurrence of the corresponding REGULATORY APPROVAL MILESTONE.

6.3 Sales Milestone Payments. AXSOME shall pay to PFIZER the SALES MILESTONE PAYMENTS within [\*\*\*] ([\*\*\*) [\*\*\*] after the end of the CALENDAR QUARTER in which the applicable SALES MILESTONE is achieved.

6.4 Royalty Payments. AXSOME shall pay to PFIZER the ROYALTY PAYMENTS within [\*\*\*] ([\*\*\*) [\*\*\*] after the end of the applicable CALENDAR QUARTER.

6.5 Significant Transaction Payments. AXSOME shall pay all SIGNIFICANT TRANSACTION PAYMENTS within [\*\*\*] ([\*\*\*) [\*\*\*] of receipt by AXSOME of each payment of consideration that corresponds to the applicable SIGNIFICANT TRANSACTION.

6.6 Other Payments. All other payments under this AGREEMENT that are not otherwise set forth in this Section 6 shall, unless otherwise specified, be paid by AXSOME to PFIZER within [\*\*\*] ([\*\*\*) [\*\*\*] following receipt of an invoice thereof from PFIZER.

6.7 Late Payments. Any amount required to be paid by a PARTY hereunder which is not paid on the date due shall bear interest at the highest rate permitted by APPLICABLE LAW, but no more than at [\*\*\*] percent ([\*\*\*) above the thirty (30) day U.S. prime rate effective for the date such payment was due, as reported in the Wall Street Journal. Such interest shall be computed on the basis of a year of three hundred sixty (360) days for the actual number of days payment is delinquent.

6.8 Method of Payments. All payments by AXSOME to PFIZER shall be made by wire transfer via immediately available funds in U.S. Dollars to credit the bank account set forth below or such other bank account as designated by PFIZER in writing to AXSOME at least thirty (30) days before payment is due. Any payment which falls due on a date which is not a BUSINESS DAY may be made on the next succeeding BUSINESS DAY.

Bank Name:	[***]
Bank Country:	[***]
Bank Address:	[***]
Bank Account Number:	[***]
Routing / ABA Number	[***]

6.9 Taxes6.9.1 General. It is understood and agreed between the PARTIES that any payments made under this AGREEMENT are exclusive of any value added or similar tax (“VAT”), which shall be added thereon as applicable. In the event any payments made by AXSOME to PFIZER pursuant to this AGREEMENT become subject to withholding taxes under the APPLICABLE LAWS of any jurisdiction, AXSOME shall deduct and withhold the amount of such taxes for the account of PFIZER to the extent required by APPLICABLE LAW and such amounts payable to PFIZER shall be reduced by the amount of taxes deducted and withheld, which shall be treated as paid to PFIZER in accordance with this AGREEMENT. To the extent that AXSOME is required to deduct and withhold taxes on any payments under this AGREEMENT, AXSOME shall pay the amounts of such taxes to the proper GOVERNMENTAL AUTHORITY in a timely manner and promptly transmit to the payee an official tax certificate or other evidence of such withholding sufficient to enable PFIZER to claim such payments of taxes. PFIZER shall provide any tax forms to AXSOME that may be reasonably necessary in order for AXSOME not to withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Each PARTY shall provide the other with reasonable assistance to enable the recovery, as permitted by APPLICABLE LAW, of withholding taxes, VAT, or similar obligations resulting from payments made under this AGREEMENT, such recovery to be for the benefit of the PARTY bearing such withholding tax or VAT.

6.9.2 Tax Actions. Notwithstanding anything in this Agreement to the contrary, if an action, including but not limited to any assignment or sublicense of its rights or obligations under this AGREEMENT, or any failure to comply with APPLICABLE LAWS or filing or record retention requirements (each a “TAX ACTION”) by a PARTY leads to the imposition of withholding tax liability or VAT on the other Party that would not have been imposed in the absence of a TAX ACTION or in an increase in such liability above the liability that would have been imposed in the absence of such TAX ACTION, then (i) the sum payable by the PARTY that caused the TAX ACTION (in respect of which such deduction or withholding is required to be made) shall be increased to the extent necessary to ensure that the other PARTY receives a sum equal to the sum which it would have received had no TAX ACTION occurred and (ii) the sum payable by the PARTY that caused a TAX ACTION (in respect of which such deduction or withholding is required to be made) shall be made to the other PARTY after deduction of the amount required to be so deducted or withheld, which deducted or withheld amount shall be remitted in accordance with APPLICABLE LAW. For the avoidance of doubt, a PARTY shall only be liable for increased payments pursuant to this Section 6.9.2 to the extent such PARTY engaged in a TAX ACTION that created or increased a withholding tax or VAT on the other PARTY.

6.9.3 Cooperation. The PARTIES agree to cooperate and produce on a timely basis any tax forms or reports, including an IRS Form W-8BEN, reasonably requested by the other PARTY in connection with any payment made by AXSOME to PFIZER under this AGREEMENT.



7. Records; Audit Rights

Relevant Records. AXSOME shall maintain and if applicable, ensure that its AFFILIATES and SUBLICENSEES maintain accurate financial books and records pertaining to COMMERCIALIZATION of the PRODUCTS by AXSOME, its AFFILIATES or the applicable SUBLICENSEES, including any and all calculations of the payments under this AGREEMENT (collectively, "RELEVANT RECORDS"). AXSOME shall maintain the RELEVANT RECORDS for the longer of: (a) the period of time required by APPLICABLE LAW, or (b) three (3) years following expiration or termination of this AGREEMENT.

7.2 Audit Request. PFIZER shall have the right during the term of this AGREEMENT and for twelve (12) months thereafter to engage, at its own expense, an independent auditor reasonably acceptable to AXSOME and subject to obligations of confidentiality imposed by AXSOME, which shall be in accordance with industry standards, to examine the RELEVANT RECORDS from time-to-time but no more frequently than once every twelve (12) months, as may be necessary to verify compliance of the payments made by AXSOME with the terms of this AGREEMENT. Such audit shall be requested in writing at least seven (7) days in advance and shall be conducted during AXSOME's normal business hours and otherwise in a manner that minimizes any interference to AXSOME's business operations.

7.3 Audit Fees and Expenses. PFIZER shall bear any and all fees and expenses it may incur in connection with any such audit of the RELEVANT RECORDS; provided, however, in the event an audit reveals an underpayment by AXSOME of more than [\*\*\*] percent ([\*\*\*]%) as to the period subject to the audit, AXSOME shall reimburse PFIZER for any reasonable and documented out-of-pocket costs and expenses of the audit within thirty (30) days after receiving invoices thereof, PFIZER shall have the right to examine the RELEVANT RECORDS of AXSOME up to once every six (6) months for the two (2) year period following the audit revealing such underpayment.

7.4 Payment of Deficiency; Overpayment. If any audit establishes that AXSOME underpaid any amounts due to PFIZER under this AGREEMENT, then AXSOME shall pay PFIZER any such deficiency within thirty (30) days after receipt of written notice thereof. For the avoidance of doubt, such payment will be considered a late payment pursuant to Section 6.7. If any audit establishes that AXSOME overpaid any amounts, then PFIZER shall credit the amount of such overpayment against future amount due under the AGREEMENT less the cost of the audit or refund such overpayment less the cost of the audit to AXSOME if no further amounts are due under the AGREEMENT within forty-five (45) days after receipt of written notice thereof.

8. Intellectual Property

8.1 Pre-Existing IP. Subject only to the rights expressly granted to the other PARTY under this AGREEMENT, each PARTY shall retain all rights, title and interests in and to any INTELLECTUAL PROPERTY RIGHTS that are owned, licensed or sublicensed by such PARTY prior to or independent of this AGREEMENT.

8.2 Ownership of Patents; Assignment of Patents. During the TERM, title and ownership of the LICENSED PATENT RIGHTS shall remain with PFIZER or its

AFFILIATES as determined by PFIZER in its sole discretion. PFIZER shall be entitled to transfer or have transferred ownership and title of the LICENSED PATENT RIGHTS to any of its AFFILIATES or to itself, as it deems necessary or desirable in its sole discretion, without the need to obtain prior approval from AXSOME; provided, however that such AFFILIATE is bound to the provisions of this AGREEMENT.

### 8.3 Patent Prosecution and Maintenance

8.3.1 Axsome Responsibility. Upon the EFFECTIVE DATE, AXSOME shall be solely responsible for (subject to the provisions of Section 8.3.7 relating to the failure to prosecute or maintain) at its sole cost and expense and shall:

(a) Prosecute on behalf of and in the name of PFIZER or PFIZER's AFFILIATES, as applicable, the LICENSED PATENT RIGHTS, including performance of all actions necessary and related to reexaminations, reissues, interferences, inter partes review, oppositions, pre and post grant proceedings, patent term extensions, patent term restorations, patent term adjustments and the like thereof (the "PATENT PROSECUTION"); and

(b) Pay annuities and take all other actions necessary to maintain the LICENSED PATENT RIGHTS in force and effect (the "PATENT MAINTENANCE").

8.3.2 External Patent Counsel. Within thirty (30) days of the EFFECTIVE DATE, PFIZER shall, if applicable, authorize and instruct any of its external patent counsel and agents managing any of PATENT PROSECUTION and PATENT MAINTENANCE to communicate with and act on the instructions of AXSOME regarding the further PATENT PROSECUTION and PATENT MAINTENANCE. The costs and expenses of any activities relating to such instructions shall be billed solely and directly to AXSOME and AXSOME shall be solely responsible for such costs and expenses.

8.3.3 Powers of Attorney. Within thirty (30) days of the EFFECTIVE DATE, PFIZER shall execute and have its AFFILIATES, if applicable, execute all powers of attorney and the like needed to effectuate the purposes of this Section 8.3.

8.3.4 Documents. Within sixty (60) days of the EFFECTIVE DATE, PFIZER shall make COMMERCIALY REASONABLE EFFORTS to provide to AXSOME all documents in its possession relating to the PATENT PROSECUTION and the PATENT MAINTENANCE.

8.3.5 Pfizer Right to Comment; Providing Information. AXSOME shall provide PFIZER with copies of applicable documents and a reasonable opportunity (at least thirty (30) days) to review and provide comments to AXSOME with respect to any office actions or other communications of any applicable GOVERNMENTAL AUTHORITY, responses to such office actions or communications and the like relating to the PATENT PROSECUTION and the PATENT MAINTENANCE. Upon request from PFIZER, AXSOME shall promptly provide PFIZER with full and complete details of all reasonably requested information relating to the PATENT PROSECUTION and the PATENT MAINTENANCE.

8.3.6 Assistance. PFIZER shall use COMMERCIALY REASONABLE EFFORTS to provide assistance to AXSOME with respect to the PATENT PROSECUTION or PATENT MAINTENANCE, subject to the following terms and conditions:

- (a) AXSOME shall make reasonable requests for such assistance; and
- (b) Any assistance provided by PFIZER shall be at AXSOME's sole cost and expense.

8.3.7 Failure to Prosecute or Maintain. With respect to any LICENSED PATENT RIGHT, in the event AXSOME elects to forgo the applicable PATENT PROSECUTION or the PATENT MAINTENANCE, or otherwise elects to terminate its license to any LICENSED PATENT RIGHTS, AXSOME shall notify PFIZER in writing of such election ("ELECTION NOTICE"). Each ELECTION NOTICE shall be provided at least forty-five (45) days prior to any applicable filing or payment due date. Upon receipt of an ELECTION NOTICE, PFIZER shall be entitled, upon written notice to AXSOME, at its sole discretion and expense, to undertake the applicable PATENT PROSECUTION or PATENT MAINTENANCE, in which case, as of the date of the applicable ELECTION NOTICE, the license granted in Section 2.1 with respect to such LICENSED PATENT RIGHT shall become non-exclusive and AXSOME will have no further rights and PFIZER will have no further obligations to LICENSEE, in respect of the PATENT PROSECUTION and PATENT MAINTENANCE thereto.

#### 8.4 Infringement; Misappropriation

8.4.1 Notification. Each PARTY will promptly notify the other PARTY in writing of any (i) actual or threatened infringement, misappropriation or other violation by a THIRD PARTY of any LICENSED IP in the FIELD and in the TERRITORY of which it becomes aware, including if such involves the filing of an ANDA under Section 505(j) of the FD&C Act or an application under Section 505(b)(2) of the FD&C Act naming a PRODUCT as a reference listed drug and including a certification under Section 505(j)(2)(A)(vii)(IV) or 505(b)(2)(A)(IV), respectively or (ii) initiation of an action for declaratory judgment against any LICENSED PATENT RIGHT in the TERRITORY (any of (i) or (ii) constituting a "THIRD PARTY INFRINGEMENT").

#### 8.4.2 Right of First Enforcement

- (a) AXSOME shall have the first right (but not the obligation), at its sole cost and expense, to control enforcement of the LICENSED IP against any THIRD PARTY INFRINGEMENT. AXSOME shall be entitled to name PFIZER as an additional party in applicable actions or proceedings if necessary in order to enable AXSOME to exercise its right to control enforcement against such THIRD PARTY INFRINGEMENT. Prior to commencing any such action, AXSOME shall consult with PFIZER and shall give due consideration to PFIZER's recommendations regarding the proposed action. AXSOME shall give PFIZER timely notice of any proposed settlement of any such action or proceedings related to a THIRD

PARTY INFRINGEMENT. AXSOME shall not, without the prior written consent of PFIZER, which consent shall not be unreasonably withheld or delayed, enter into any settlement that would: (i) adversely affect the validity, enforceability or scope of any of the LICENSED PATENT RIGHTS, or (ii) admits non-infringement of any LICENSED PATENT RIGHTS. AXSOME shall not, without the prior written consent of PFIZER, which PFIZER shall have sole discretion in granting, enter into any settlement that (i) gives rise to liability of PFIZER or its AFFILIATES, or (ii) impairs PFIZER's rights in any LICENSED IP or this AGREEMENT.

(b) If AXSOME does not, with respect to its first right of enforcement under Section 8.4.2(a), obtain agreement from the alleged infringer to desist, or fails or refuses to initiate an infringement action by the earlier of (i) one hundred-twenty (120) days following AXSOME's receipt of notice of the alleged infringement or (ii) fifteen (15) days before the expiration date for filing such actions, then PFIZER shall have the right, at its sole discretion, to control such enforcement of the LICENSED IP at its sole expense, and notwithstanding the provisions of Section 8.4.3, shall be entitled to retain any and all applicable recoveries; provided, however PFIZER shall not, without the prior written consent of AXSOME, which AXSOME consent shall not be unreasonably withheld, enter into any settlement that (i) gives rise to liability of AXSOME or its AFFILIATES, or (ii) impairs AXSOME's rights in any LICENSED IP or this AGREEMENT.

8.4.3 Recoveries. Subject to Subsection (b) of Section 8.4.2, any recoveries resulting from an action relating to a claim of THIRD PARTY INFRINGEMENT shall first be applied to reimburse each PARTY's costs and expenses incurred in connection therewith. If AXSOME institutes an action or proceeding, any remaining recoveries shall be retained by (or if received by PFIZER, paid to) AXSOME; provided, however, PFIZER shall be entitled to ROYALTY PAYMENTS on such remaining recoveries of [\*\*\*] percent ([\*\*\*]%).

9. Confidentiality

9.1 Definition. "CONFIDENTIAL INFORMATION" of a PARTY means (i) this AGREEMENT including its terms and conditions and, subject to disclosure pursuant to the provisions of Section 15.2, the existence thereof; and (ii) all other proprietary information and data of a financial, commercial or technical nature that such PARTY or any of its AFFILIATES has supplied or otherwise made available to the other PARTY, any of its AFFILIATES or any of their RECIPIENTS, in written, visual, or electronic form or if disclosed orally, summarized in writing and provided to the other PARTY within thirty (30) days after such disclosure. Subject to the terms of this AGREEMENT, all LICENSED KNOW-HOW shall be considered the CONFIDENTIAL INFORMATION of PFIZER.

Confidential Information shall not include information that: (a) is, at the time of disclosure or becomes, after the time of disclosure, known to the public or part of the public domain through no breach of this AGREEMENT by the receiving PARTY; (b) was known to, or was otherwise in the possession of, the receiving PARTY prior to the time of

disclosure by the disclosing PARTY; (c) is disclosed to the receiving PARTY on a non-confidential basis by a THIRD PARTY who is entitled to disclose it without breaching any confidentiality obligation to the disclosing PARTY; or (d) is independently developed by or on behalf of the receiving PARTY or any of its AFFILIATES, as evidenced by its written records.

9.2 Obligations. The receiving PARTY shall protect all CONFIDENTIAL INFORMATION against unauthorized disclosure to THIRD PARTIES with the same degree of care as the receiving PARTY uses for its own similar information, but in no event less than a reasonable degree of care. The receiving PARTY shall not use the CONFIDENTIAL INFORMATION of the other PARTY for any purpose other than as provided for in this AGREEMENT (which includes the exercise of any rights or the performance of any obligations hereunder). The receiving PARTY may disclose the CONFIDENTIAL INFORMATION to its AFFILIATES and to their respective directors, officers, employees, subcontractors, current and prospective sublicensees, consultants, attorneys, accountants, banks, acquirers and investors (collectively, "RECIPIENTS") who have a need to know such information for purposes related to this AGREEMENT, provided that the receiving PARTY shall hold such RECIPIENTS to written obligations of confidentiality and non-use with terms and conditions at least as restrictive as those set forth in this AGREEMENT. All obligations of confidentiality and non-use under this Agreement shall survive expiration or termination of this Agreement for a period of seven (7) years, except that with respect to trade secrets, the obligations of confidentiality and non-use shall survive for so long as the applicable CONFIDENTIAL INFORMATION remains a trade secret.

### 9.3 Exceptions

9.3.1 Disclosure Required by Law. Notwithstanding the restrictions set forth in this Section 9, the receiving PARTY shall have the right to disclose CONFIDENTIAL INFORMATION of the disclosing PARTY to the extent required under APPLICABLE LAWS or a court order or other governmental order, including regulations applicable to the public sale of securities, provided that in the receiving PARTY: (i) provides the disclosing PARTY with prompt notice of such disclosure requirement if legally permitted, (ii) affords the disclosing PARTY an opportunity to oppose, limit or secure confidential treatment for such required disclosure, to the extent practicable, and (iii) if the disclosing PARTY is unsuccessful in its efforts pursuant to subsection (ii), discloses only that portion of the CONFIDENTIAL INFORMATION that the receiving PARTY is legally required to disclose as advised by the receiving PARTY's legal counsel.

9.3.2 Disclosure to Assignee of Payments. PFIZER shall be entitled to disclose to a THIRD PARTY the CONFIDENTIAL INFORMATION of AXSOME for the purposes for discussing, negotiating and consummating a transaction with a THIRD PARTY to assign, pledge or otherwise transfer its rights to receive some or all of the MILESTONE PAYMENTS or the ROYALTIES PAYMENTS payable hereunder, provided that such THIRD PARTIES owes the obligation to PFIZER of confidentiality and non-use with terms and conditions at least as restrictive as those set forth in this AGREEMENT.

9.3.3 Disclosure for Regulatory Filings, Patent Filings, or Investment. Notwithstanding anything herein, in addition to other disclosures allowed under this Article 9, AXSOME shall be entitled to also disclose the LICENSED KNOW-HOW to REGULATORY AUTHORITIES as reasonably needed to file and maintain REGULATORY APPROVALS FOR COMPOUNDS or PRODUCTS, in connection with any patent filing or to potential acquirors of AXSOME or of the PRODUCTS and their respective professional advisors, provided that any such disclosure shall be subject to a written confidentiality agreement with terms of non-disclosure no less restrictive than those set forth in this AGREEMENT.

9.4 Right to Injunctive Relief. Each PARTY agrees that any breach of this Section 9 may cause irreparable harm to the other PARTY and shall entitle such other PARTY, in addition to any other remedies available to it (subject to the terms of this AGREEMENT), the right to seek injunctive relief enjoining such action.

9.5 Ongoing Obligation of Confidentiality. Upon expiration or termination of this AGREEMENT, the receiving PARTY shall, and shall cause its RECIPIENTS to, destroy or return (as requested by the disclosing PARTY) any CONFIDENTIAL INFORMATION of the disclosing PARTY, except that the receiving PARTY (a) may retain a single copy of CONFIDENTIAL INFORMATION for the sole purpose of ascertaining its rights and responsibilities in respect of such information and (b) shall not be required to destroy any computer files stored securely by the receiving PARTY that are created by automatic system back up.

10. Right of First Negotiation; Significant Transactions

10.1 The following definitions shall apply to this Section 10:

10.1.1 “ROFN NEGOTIATION PERIOD” means a period beginning on the date of the ROFN EXERCISE NOTICE and ending on the date that is [\*\*\*] ([\*\*\*)] [\*\*\*] thereafter.

10.1.2 “ROFN NOTICE PERIOD” means a period beginning on the date of the ROFN OFFER NOTICE and ending on the date that is [\*\*\*] ([\*\*\*)] [\*\*\*] thereafter.

10.2 AXSOME hereby grants to PFIZER an exclusive right of first negotiation with respect to any newly proposed SIGNIFICANT TRANSACTION, in accordance with the terms and conditions set forth in this Section 10 (the “ROFN”).

10.3 Prior to entering into a negotiation with a THIRD PARTY for a proposed SIGNIFICANT TRANSACTION, AXSOME shall provide PFIZER with (a) written notice of the nature of the proposed SIGNIFICANT TRANSACTION and (b) a summary of the most recent material clinical data for the PRODUCT within AXSOME’s possession and control (such notice together with the related information (the “ROFN OFFER NOTICE”).

10.4 PFIZER shall have the right to enter into exclusive negotiations with AXSOME for the newly proposed SIGNIFICANT TRANSACTION by giving AXSOME written notice thereof (the “ROFN EXERCISE NOTICE”), provided that PFIZER has given the ROFN EXERCISE NOTICE on or before the end of the applicable ROFN NOTICE PERIOD. In the event PFIZER does not provide a ROFN EXERCISE NOTICE within the ROFN

NOTICE PERIOD, the ROFN shall expire and shall be of no further force and effect, subject to provisions set forth in this Article 10.

10.5 During the ROFN NEGOTIATION PERIOD, the PARTIES shall engage in good faith negotiations for the proposed SIGNIFICANT TRANSACTION and shall endeavor to consummate the SIGNIFICANT TRANSACTION prior to the end of the ROFN NEGOTIATION PERIOD. The information communicated between the PARTIES during such negotiations shall be considered CONFIDENTIAL INFORMATION of both PARTIES.

10.6 During the ROFN NOTICE PERIOD and the ROFN NEGOTIATION PERIOD, AXSOME shall not engage in negotiations of the proposed SIGNIFICANT TRANSACTION with any THIRD PARTY.

10.7 In the event that a proposed SIGNIFICANT TRANSACTION has not been consummated between the PARTIES by the end of the of the ROFN NEGOTIATION PERIOD, AXSOME shall be entitled after such time to engage in negotiations with a THIRD PARTY for the proposed SIGNIFICANT TRANSACTION, provided that for a period of [\*\*\*] ([\*\*\*) [\*\*\*] following the end of the ROFN NEGOTIATION PERIOD, AXSOME shall not enter into such SIGNIFICANT TRANSACTION with a THIRD PARTY wherein the material terms and conditions thereof are less favorable to AXSOME as compared to the applicable terms and conditions proposed by PFIZER to AXSOME during the ROFN NEGOTIATION PERIOD.

10.8 If at any time between [\*\*\*] and [\*\*\*] any [\*\*\*], then such proposed SIGNIFICANT TRANSACTION shall be deemed a newly proposed SIGNIFICANT TRANSACTION subject to a new ROFN and to all other rights as set forth in this Section 10, including the right to notice and to exclusive negotiation.

10.9 Within five (5) BUSINESS DAYS of the final execution, closing or otherwise consummation of a SIGNIFICANT TRANSACTION, AXSOME shall provide PFIZER with written notification including details regarding the material terms and conditions of the SIGNIFICANT TRANSACTION, subject to redactions for confidential information.

## 11. Representations, Warranties and Covenants

11.1 Representations and Warranties by Each Party. Each PARTY represents and warrants to the other PARTY that as of the EFFECTIVE DATE:

11.1.1 it is a corporation or company, as applicable, duly organized, validly existing, and in good standing under the laws of its jurisdiction of formation;

11.1.2 it has full corporate power and authority to execute, deliver, and perform under this Agreement, and has taken all corporate action required by APPLICABLE LAW and its organizational documents to authorize the execution and delivery of this AGREEMENT and the consummation of the transactions contemplated by this AGREEMENT;

11.1.3 this AGREEMENT constitutes a valid and binding agreement enforceable against it in accordance with its terms; and

11.1.4 the execution and delivery of this AGREEMENT and all other instruments and documents required to be executed pursuant to this AGREEMENT, and the

consummation of the transactions contemplated hereby do not and shall not: (i) conflict with or result in a breach of any provision of its organizational documents, (ii) result in a breach of any agreement to which it is a party that would impair the performance of its obligations hereunder; or (iii) cause it to violate any APPLICABLE LAW.

11.2 Representations and Warranties by Pfizer. PFIZER represents and warrants to AXSOME that as of the EFFECTIVE DATE:

11.2.1 PFIZER (or one or more of its AFFILIATES) is or are the sole owner of the entire right, title and interest in and to the LICENSED IP free and clear from any liens, mortgages, security interests or other encumbrances;

11.2.2 PFIZER has the right to grant the licenses and other rights purported to be granted to AXSOME under this AGREEMENT; and

11.2.3 PFIZER has no KNOWLEDGE of having received any written notice from any THIRD PARTY claiming a right, title, interest, ownership, misappropriation or other proprietary rights to the LICENSED IP of such THIRD PARTY.

11.3 Representations, Warranties and Covenants by AXSOME

11.3.1 AXSOME covenants to PFIZER that it shall comply with all APPLICABLE LAW with respect to the performance of its rights and obligations hereunder; and

11.3.2 AXSOME represents and warrants that it is not prohibited by contractual obligation or by APPLICABLE LAW from DEVELOPING, MANUFACTURING, COMMERCIALIZING or otherwise EXPLOITING the COMPOUNDS or the PRODUCTS in the TERRITORY pursuant to this AGREEMENT.

11.4 No Action Required Which Would Violate Law11.5 . In no event shall either PARTY be obligated under this AGREEMENT to take any action or omit to take any action that such PARTY believes, in good faith, would cause it to violate any APPLICABLE LAW.

11.6 No Other Warranties11.7 . EXCEPT AS EXPRESSLY STATED IN THIS SECTION 11, NEITHER PARTY MAKES ANY REPRESENTATIONS OR EXTENDS ANY WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, STATUTORY OR OTHERWISE, INCLUDING BUT NOT LIMITED TO WARRANTIES OF TITLE, NON-INFRINGEMENT, VALIDITY, ENFORCEABILITY, MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE, AND ANY INFORMATION OR MATERIALS PROVIDED BY PFIZER OR ITS AFFILIATES IS MADE AVAILABLE ON AN "AS IS" BASIS WITHOUT WARRANTY WITH RESPECT TO COMPLETENESS, COMPLIANCE WITH REGULATORY STANDARDS OR REGULATIONS OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER KIND OF WARRANTY WHETHER EXPRESS OR IMPLIED.

12. Indemnification

12.1 Indemnification by Axsome. AXSOME agrees to indemnify, hold harmless and defend PFIZER and its AFFILIATES, and their respective officers, directors, employees,



contractors, agents and assigns (collectively, "PFIZER INDEMNITEES"), from and against any CLAIMS by a THIRD PARTY against a PFIZER INDEMNITEE (including reasonable costs of defense) arising or resulting from: (a) defects in the manufacture of any COMPOUND or any PRODUCT and defects in any PRODUCT; (b) AXSOME's, its AFFILIATES', contractors or the SUBLICENSEES' (if applicable) use of any COMPOUND or any PRODUCT; (c) the DEVELOPMENT of a COMPOUND or PRODUCT by AXSOME, its AFFILIATES, contractors or the SUBLICENSEES (if applicable), (d) the COMMERCIALIZATION of a COMPOUND or PRODUCT by AXSOME, its AFFILIATES, contractors or SUBLICENSEES (if applicable), (e) the negligence, recklessness or wrongful intentional acts or omissions of AXSOME, its AFFILIATES, contractors or the SUBLICENSEES (if applicable) in performing any activities under this AGREEMENT, (f) breach by AXSOME of any representation, warranty or covenant as set forth in this AGREEMENT or (g) breach by AXSOME of the scope of the license set forth in Section 2.1, except in each case (a)-(g) to the extent such CLAIM arises or results from the negligence, recklessness or wrongful intentional acts or omissions of any PFIZER INDEMNITEE or a breach by PFIZER of any representation, warranty or covenant as set forth in this AGREEMENT.

12.2 Indemnification by Pfizer. PFIZER agrees to indemnify, hold harmless and defend AXSOME and its AFFILIATES, and their respective officers, directors, employees, sublicensees, agents and assigns (collectively, "AXSOME INDEMNITEES"), from and against any CLAIMS by a THIRD PARTY against an AXSOME INDEMNITEE to the extent arising or resulting from (a) the negligence, recklessness or wrongful intentional acts or omissions of PFIZER or its AFFILIATES; (b) the breach by PFIZER of any representation, warranty or covenant as set forth in this AGREEMENT, (c) acts or omissions of PFIZER or its AFFILIATES in the MANUFACTURE or COMMERCIALIZING of the COMPOUNDS and products containing the COMPOUNDS that occur prior to the EFFECTIVE DATE, except in each case (a), (b) or (c) to the extent such CLAIM arises or results from (i) the negligence, recklessness or wrongful intentional acts or omissions of any AXSOME INDEMNITEE or (ii) breach by AXSOME of any representation, warranty or covenant as set forth in this AGREEMENT.

12.3 Indemnification Procedure. In connection with any CLAIM for which a PARTY (the "INDEMNITEE") seeks indemnification from the other PARTY (the "INDEMNITOR") pursuant to this AGREEMENT, the INDEMNITEE shall: (a) give the INDEMNITOR prompt written notice of the CLAIM; provided, however, that failure to provide such notice shall not relieve the INDEMNITOR from its liability or obligation hereunder, except to the extent of any material prejudice as a direct result of such failure; (b) cooperate with the INDEMNITOR, at the INDEMNITOR's expense, in connection with the defense and settlement of the CLAIM; and (c) permit the INDEMNITOR to control the defense and settlement of the CLAIM; provided, however, that the INDEMNITOR may not settle the CLAIM without the INDEMNITEE's prior written consent, which shall not be unreasonably withheld or delayed, in the event that such settlement materially adversely impacts the INDEMNITEE's rights or obligations.

Further, the INDEMNITEE shall have the right to participate (but not control) and be represented in any suit or action by legal counsel of its selection and at its own expense.

13. Limitation of Liability; Consequential Damages Waiver.

13.1 EXCEPT FOR A BREACH OF SECTION 9 (confidentiality) OR OBLIGATIONS ARISING UNDER SECTION 12 (indemnification), NEITHER PARTY SHALL BE LIABLE TO THE OTHER PARTY FOR ANY INDIRECT, CONSEQUENTIAL, SPECIAL, EXEMPLARY OR PUNITIVE DAMAGES, INCLUDING DAMAGES FOR LOST PROFITS OR LOST REVENUES, REGARDLESS OF WHETHER IT HAS BEEN INFORMED OF THE POSSIBILITY OR LIKELIHOOD OF SUCH DAMAGES OR THE TYPE OF CLAIM, CONTRACT OR TORT (INCLUDING NEGLIGENCE).

13.2 Liability Cap

13.2.1 "CAP" means the sum of [\*\*\*], [\*\*\*] and [\*\*\*] paid by AXSOME to PFIZER during the [\*\*\*] ([\*\*\*) [\*\*\*] immediately preceding the event giving rise to the applicable CLAIM.

13.2.2 IN NO EVENT SHALL PFIZER'S LIABILITY FOR DAMAGES IN CONNECTION WITH THIS AGREEMENT EXCEED THE CAP, REGARDLESS OF WHETHER PFIZER HAS BEEN INFORMED OF THE POSSIBILITY OR LIKELIHOOD OF SUCH DAMAGES OR THE TYPE OF CLAIM, CONTRACT OR TORT (INCLUDING NEGLIGENCE); PROVIDED, HOWEVER, THAT NOTHING HEREIN SHALL LIMIT PFIZER'S LIABILITY FOR DAMAGES RESULTING FROM ANY FRAUD OF PFIZER THAT OCCURRED PRIOR TO OR ON THE EFFECTIVE DATE.

14. Term; Termination

14.1 Term. The term of this AGREEMENT shall commence as of the EFFECTIVE DATE and shall expire on a PRODUCT-by-PRODUCT basis upon the expiration of the last-to-expire ROYALTY TERM for such PRODUCT (the "TERM"). Upon such expiration, the license granted by PFIZER to AXSOME under Section 2.1 shall become non-exclusive, fully-paid, royalty free, perpetual and irrevocable.

14.2 Termination for Cause. Each PARTY shall have the right, without prejudice to any other remedies available to it at law or in equity, to terminate this AGREEMENT upon written notice to the other PARTY in the event the other PARTY materially breaches any of its obligations hereunder and fails to cure such breach within sixty (60) days of receiving notice thereof; provided, however, if such breach is capable of being cured, but cannot be cured within such sixty (60) day period, and the breaching PARTY initiates actions to cure such breach within such period and thereafter diligently pursues such actions, the breaching PARTY shall have such additional period as is reasonable to cure such breach, but in no event will such additional period exceed ninety (90) days. Any termination by a PARTY under this Section 14.2 shall be without prejudice to any damages or other legal or equitable remedies to which it may be entitled from the other PARTY. For the avoidance of doubt, AXSOME's failure to use COMMERCIALY REASONABLE EFFORTS to DEVELOP and COMMERCIALIZE the PRODUCT in accordance with Section 4.2 or failure to make

a MILESTONE PAYMENT or ROYALTY PAYMENT shall constitute a material breach by AXSOME under this AGREEMENT.

#### 14.3 Termination for a Bankruptcy Event

14.3.1 Termination Rights. PFIZER shall have the right to terminate this AGREEMENT in the event of a BANKRUPTCY EVENT of AXSOME.

14.3.2 Rights to Intellectual Property. All rights and licenses granted under or pursuant to this AGREEMENT under Section 2.1, and shall otherwise be deemed to be, for purposes of Section 365(n) of the BANKRUPTCY CODE, licenses of rights to “intellectual property” as defined under Section 101 of the BANKRUPTCY CODE. The PARTIES agree that either PARTY shall retain and may fully exercise all of its rights and elections under the BANKRUPTCY CODE. The PARTIES further agree that in the event of a rejection of this AGREEMENT by AXSOME in any bankruptcy proceeding by or against AXSOME under the BANKRUPTCY CODE, (a) PFIZER shall be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property licensed by PFIZER to AXSOME, which, if not already in PFIZER’s possession, shall be promptly delivered to it upon PFIZER’s written request therefore, and (b) AXSOME shall not interfere with PFIZER’s rights to intellectual property and all embodiments of intellectual property, and shall assist and not interfere with PFIZER in obtaining intellectual property and all embodiments of intellectual property from another entity. The term “embodiments” of intellectual property includes all tangible, intangible, electronic or other embodiments of rights and licenses hereunder, including all compounds and products embodying intellectual property, filings with REGULATORY AUTHORITIES and related rights, and LICENSED IP.

14.4 Termination for Convenience. After the first anniversary of the EFFECTIVE DATE, AXSOME shall have the right in its sole discretion and without cause to terminate this AGREEMENT in its sole and absolute discretion without any cause subject to ninety (90) days prior written notice to PFIZER, provided such notice is given no earlier than the date of such first anniversary.

#### 14.5 Effects of Termination

14.5.1 Termination by Axsome for Cause. In the event that AXSOME terminates this AGREEMENT pursuant to Section 14.2 (for cause) the following shall apply:

(a) Rights and Obligations. Except as otherwise provided herein, all rights and obligations of each PARTY hereunder shall cease.

(b) Licenses. The licenses granted to AXSOME pursuant to Section 2.1 but subject to Section 2.3 (retained rights) shall become perpetual and irrevocable.

14.5.2 Termination by Pfizer for Cause or Bankruptcy Event; Termination by Axsome for Convenience. In the event that PFIZER terminates this AGREEMENT pursuant to Section 14.2 (for cause) or Section 14.3 (for bankruptcy) or AXSOME

terminates this AGREEMENT pursuant to Section 14.4 (for convenience) the following shall apply:

(a) Rights and Obligations. Except as otherwise provided herein, all rights and obligations of each PARTY hereunder shall cease, including, subject to Subsection (c) of this Section 14.5.2, the licenses granted to AXSOME pursuant to Section 2.1.

(b) Transition. During the notice period provided in Section 14.2(termination for cause) or Section 14.4 (termination for convenience), as applicable to such termination, or as soon as practicable upon notice of termination pursuant to Section 14.3 (for bankruptcy):

(i) Transition Plan. Upon PFIZER's request, the PARTIES shall negotiate a transition plan that includes, at a minimum, a plan for accomplishing the activities described in this Section 14.5.2(b).

(ii) Technology Transfer. Upon PFIZER's request, AXSOME shall return to PFIZER or destroy all LICENSED KNOW-HOW transferred to AXSOME as of the effective date of termination. For clarity, AXSOME shall have no obligation to transfer any KNOW-HOW or technology developed under the AGREEMENT during the TERM.

(c) Sublicense Survival. Each SUBLICENSEE (if applicable) shall be entitled, upon request by the applicable SUBLICENSEE, to have the applicable SUBLICENSE survive the termination of this AGREEMENT and become a direct license from PFIZER, under the terms of this AGREEMENT applicable to the scope of such SUBLICENSE, on the condition that: (i) the SUBLICENSEE is not then in breach of its SUBLICENSE; and (ii) the SUBLICENSEE cures any the material breach by AXSOME, if such breach is a failure to pay any amounts due, and with respect to all other breaches, if such breach is applicable to the scope of the applicable SUBLICENSE, within sixty (60) days following the termination of this AGREEMENT or such longer period agreed by PFIZER and the applicable SUBLICENSEE.

14.6 Survival. Expiration or termination of this AGREEMENT shall not relieve the PARTIES of any obligation accruing hereunder prior to such expiration or termination. Without limiting the foregoing, the provisions of Sections 1 (definitions; interpretation), 2.3 (retained rights), 2.4 (residuals), 6 (payments), 7 (records; audit rights), 8.1 (pre-existing IP), 8.2 (ownership and assignment of patents), 9 (confidentiality), 11 (representations, warranties and covenants), 12 (indemnification), 13 (limitation of liability), 14.2 (termination for cause), 14.5 (effects of termination), 14.6 (survival), 15 (use of names, press releases, publications), 16 (insurance), 17 (dispute resolution), 18.1 (assignment), 18.2 (severability), 18.3 (governing law), 18.5 (waivers and amendments)

18.7 (successors and assigns), and 18.8 (notices) shall survive expiration or termination of this Agreement.

15. Use of Names; Press Releases; Publications

15.1 Use of Names. Neither PARTY (nor any of its AFFILIATES or agents) will use the registered or unregistered trademarks, service marks, trade dress, trade names, logos, insignia, domain names, symbols or designs of the other PARTY or its AFFILIATES in any press release, publication or other form of promotional disclosure without the prior written consent of the other PARTY in each instance.

15.2 Press Releases. The PARTIES agree that on the EFFECTIVE DATE, each PARTY may issue a press release as set forth in Schedule 15.2. Thereafter, if either PARTY desires to issue any press release or other public statement, whether written, electronic, oral or otherwise, disclosing the existence of this AGREEMENT, or the terms and conditions hereof, it shall first obtain the prior written consent of the other PARTY, such consent not to be unreasonably withheld or delayed; notwithstanding the foregoing, neither PARTY will be prevented from complying with or be required to obtain the written consent of the other PARTY in order to comply with any duty of disclosure it may have pursuant to APPLICABLE LAW or the rules of any recognized stock exchange (including filing a copy of this AGREEMENT or any information related thereto) so long as the disclosing PARTY provides the other PARTY at least ten (10) BUSINESS DAYS prior written notice to the extent practicable and only discloses information to the extent required by APPLICABLE LAW or the rules of any recognized stock exchange. The provisions of this Section 15.2 shall not be deemed to prohibit AXSOME from public disclosure of aspects of its business relating to the DEVELOPMENT or COMMERCIALIZATION of the COMPOUNDS or the PRODUCTS in the TERRITORY, but subject to AXSOME's obligations of confidentiality under Section 9.

15.3 Publications. During the TERM, AXSOME shall have the right to publish academic, scientific or medical publications or public presentations that relate to the DEVELOPMENT of the COMPOUNDS or the PRODUCTS, but subject to AXSOME's obligations of confidentiality under Section 9. AXSOME shall comply with standard academic practice regarding authorship of scientific publications and recognition of contribution of other parties in any publication governed by this Section 15.3, including International Committee of Medical Journal Editors standards regarding authorship and contributions.

16. Insurance

16.1 Insurance Requirements. AXSOME shall maintain until the later of (a) three (3) years after termination or expiration of this AGREEMENT or (b) the date that all statutes of limitation covering claims or suits that may be instituted for personal injury based on the sale or use of the PRODUCT have expired the following insurance issued by insurers having a minimum of "A-" A.M. Best rating: (i) As of the EFFECTIVE DATE, commercial general liability insurance of not less than [\*\*\*] per occurrence and [\*\*\*] in the aggregate; (ii) prior to the initiation of a CLINICAL TRIAL of a PRODUCT, clinical trials insurance with coverage limits of not less than three million U.S. Dollars (US\$ 3,000,000) per occurrence and [\*\*\*] in the aggregate; and (iii) prior to AXSOME's commercial launch of

a PRODUCT, product liability insurance with coverage limits of not less than [\*\*\*] per occurrence and [\*\*\*] in the aggregate. The minimum level of insurance set forth herein shall not be construed to create a limit on AXSOME's liability hereunder. Such policies shall name PFIZER and its AFFILIATES as additional insured and provide a waiver of subrogation in favor of PFIZER and its AFFILIATES. Such insurance policies shall be primary and non-contributing with respect to any other similar insurance policies available to PFIZER or its AFFILIATES. Any deductibles for such insurance shall be assumed by AXSOME.

16.2 Certificates of Insurance. Upon the EFFECTIVE DATE and annually thereafter, AXSOME shall provide certificates of insurance to PFIZER, evidencing the insurance coverage required under this AGREEMENT, except that at least thirty (30) days prior to the commencement of any CLINICAL TRIAL of a PRODUCT and on each anniversary of the EFFECTIVE DATE thereafter, AXSOME shall also provide to PFIZER certificates of insurance evidencing the required insurance coverage relating thereto.

16.3 Policy Notifications. AXSOME shall ensure that PFIZER is given at least thirty (30) days prior written notice before cancellation, termination or any material change to restrict the coverage or reduce the limits afforded with respect to any insurance coverage as required under this Section 16.

17. Dispute Resolution

17.1 General. Any disputes, controversies or other claims arising out of this AGREEMENT, its interpretation, validity, performance, enforceability, breach or termination ("DISPUTES") that are not settled amicably shall be referred by sending written notice of the DISPUTE to the other PARTY for final and binding arbitration with the office of the American Arbitration Association in New York County, New York in accordance with the then-prevailing commercial arbitration rules of the American Arbitration Association.

17.2 Number of Arbitrators. The arbitration of each DISPUTE shall be settled by a panel of (3) arbitrators. Each PARTY shall select one (1) arbitrator, and such selected arbitrators shall mutually agree upon the third arbitrator. Each PARTY shall be responsible for the costs of its selected arbitrator and the PARTIES shall equally share the costs of the third arbitrator. Each arbitrator shall have no less than ten (10) years of experience in the development and commercialization of pharmaceutical products.

17.3 Powers of the Arbitrators. For each DISPUTE:

17.3.1 The arbitrators are authorized to award to the prevailing PARTY, if a prevailing party is determined by the arbitrators, such PARTY's costs and expenses, including attorneys' fees;

17.3.2 The arbitrators shall not award punitive, exemplary, or consequential damages and the arbitrators shall not apply any multiplier to any award of actual damages, except as may be required by statute;

17.3.3 The arbitrators shall have the discretion to hear and determine at any stage of the arbitration any issue asserted by any PARTY to be dispositive of any claim or counterclaim, in whole or part, in accordance with such procedure as the

arbitrators may deem appropriate, and the arbitrators may render an award on such issue; and

17.3.4 In addition to the authority conferred on the arbitrators by the rules designated in this AGREEMENT, and without prejudice to any provisional measures that may be available from a court of competent jurisdiction, the arbitrators shall have the power to grant any provisional measures that the arbitrators deems appropriate, including but not limited to provisional injunctive relief, and any provisional measures ordered by the arbitrators may, to the extent permitted by APPLICABLE LAW, be deemed to be a final award on the subject matter of the measures and shall be enforceable as such.

18. General Provisions

18.1 Assignment. Neither PARTY may assign its rights and obligations under this AGREEMENT without the other PARTY's prior written consent, except that PFIZER may assign to a THIRD PARTY its rights to receive some or all of the payments payable hereunder and each PARTY may: (a) assign its rights and obligations under this AGREEMENT or any part hereof to one or more of its AFFILIATES without the consent of the other PARTY; and (b) assign its rights and obligations under this AGREEMENT or any part hereof to its successor in interest pursuant to a merger, acquisition, reorganization, consolidation or sale of all or substantially all of the assets of the business pertaining to the subject matter of the AGREEMENT. In the event PFIZER assigns such rights to receive payments hereunder to a THIRD PARTY, any disclosure by PFIZER of reports and forecasts provided by AXSOME to PFIZER under Sections 5.5.4 and 4.3 shall be subject to the provisions of Section 9.3.2 (disclosure to assignee of payments). The assigning PARTY shall provide the other PARTY with prompt written notice of any such assignment. Any permitted assignee pursuant to clause (a) or (b) above shall assume all obligations of its assignor under this AGREEMENT, provided that no permitted assignment shall relieve the assignor of liability for its obligations hereunder. Any attempted assignment in contravention of the foregoing shall be void.

18.2 Severability. Should one or more of the provisions of this AGREEMENT become void or unenforceable as a matter of law, then such provision will be ineffective only to the extent of such prohibition or invalidity, without invalidating the remainder of this AGREEMENT, and the PARTIES agree to substitute a valid and enforceable provision therefor which, as nearly as possible, achieves the desired economic effect and mutual understanding of the PARTIES under this AGREEMENT.

18.3 Governing Law; Jurisdiction. This Agreement shall be governed by and construed under the laws in effect in the State of New York, U.S. without giving effect to any conflicts of laws provision thereof or of any other jurisdiction that would produce a contrary result. The provisions of Section 17 (arbitration) are not intended to deprive any court of competent jurisdiction with respect to its power to issue a pre-arbitral injunction, pre-arbitral attachment or other order in aid of arbitration proceedings or the enforcement of any judgment or award. In any such action, the courts of the Southern District of New York shall have non-exclusive jurisdiction over any action brought to enforce this Agreement, and each of the PARTIES hereby irrevocably: (a) submits to such non-exclusive jurisdiction for such purpose; (b) waives any objection which it may have at any

time to the laying of venue of any proceedings brought in such courts; (c) waives any claim that such proceedings have been brought in an inconvenient forum; and (d) further waives the right to object with respect to such proceedings that any such court does not have jurisdiction over such PARTY.

18.4 Force Majeure. Except with respect to delays or nonperformance caused by the negligent or intentional act or omission of a PARTY, any delay or nonperformance by such PARTY (other than payment obligations under this AGREEMENT) will not be considered a breach of this AGREEMENT to the extent such delay or nonperformance is caused by acts of God, natural disasters, acts of the government or civil or military authority, fire, floods, epidemics, quarantine, energy crises, war or riots or other similar cause outside of the reasonable control of such PARTY (each, a "FORCE MAJEURE EVENT"), provided that the PARTY affected by such FORCE MAJEURE EVENT shall promptly begin or resume performance as soon as reasonably practicable after the event has abated. If a FORCE MAJEURE EVENT prevents a PARTY from performing any of its obligations under this AGREEMENT for one hundred eighty (180) days or more, then the other PARTY may terminate this Agreement immediately upon written notice to the non-performing PARTY pursuant to Section 14.2 (termination for cause).

18.5 Waivers and Amendments. The failure of any PARTY to assert a right hereunder or to insist upon compliance with any term or condition of this AGREEMENT shall not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition by the other PARTY. No waiver shall be effective unless it has been given in writing and signed by the PARTY giving such waiver. No provision of this AGREEMENT may be amended or modified other than by a written document signed by authorized representatives of each PARTY.

18.6 Relationship of the Parties. Nothing contained in this AGREEMENT will be deemed to constitute a partnership, joint venture, or legal entity of any type between PFIZER and AXSOME, or to constitute one PARTY as the agent of the other. Moreover, each PARTY agrees not to construe this AGREEMENT, or any of the transactions contemplated hereby, as a partnership for any tax purposes. Each PARTY shall act solely as an independent contractor, and nothing in this AGREEMENT shall be construed to give any PARTY the power or authority to act for, bind, or commit the other PARTY.

18.7 Successors and Assigns. This AGREEMENT shall be binding upon and inure to the benefit of the PARTIES hereto and their respective successors and permitted assigns.

18.8 Notices. All notices, consents, waivers, and other communications under this AGREEMENT shall be in writing and shall be deemed to have been duly given when: (a) delivered by hand (with written confirmation of receipt), (b) sent by email (with written confirmation of receipt), provided that a copy is sent by an internationally recognized overnight delivery service (receipt requested), or (c) when received by the addressee, if sent by an internationally recognized overnight delivery service (receipt requested), in each



case to the appropriate addresses and email set forth below (or to such other addresses and email as a PARTY may designate by written notice):

If to PFIZER:

Pfizer Inc.  
235 East 42<sup>nd</sup> Street  
New York, NY 10017  
Attention: General Counsel

Email: [\*\*\*]

If to AXSOME:

Axsome Therapeutics, Inc.  
200 Broadway, 3rd Floor  
New York, New York 10038  
Attention: General Counsel

Email: \_\_\_\_\_

With a copy to (which shall not constitute notice or service of process):

DLA Piper LLP (US)  
51 John F. Kennedy Parkway, Suite 120  
Short Hills, New Jersey 07078  
Telephone: (973) 307-3004  
Facsimile: (973) 520-2551  
E-mail: emilio.ragosa@dlapiper.com  
Attention: Emilio Ragosa, Esq.

18.9 Further Assurances. AXSOME and PFIZER hereby covenant and agree without the necessity of any further consideration, to execute, acknowledge and deliver any and all such other documents and take any such other action as may be reasonably necessary or appropriate to carry out the intent and purposes of this Agreement.

18.10 No Third Party Beneficiary Rights. This AGREEMENT is not intended to and shall not be construed to give any THIRD PARTY any interest or rights (including, without limitation, any third party beneficiary rights) with respect to or in connection with any agreement or provision contained herein or contemplated hereby.

18.11 Entire Agreement; Confidentiality Agreement

18.11.1 This AGREEMENT, together with its Schedules, sets forth the entire agreement and understanding of the PARTIES as to the subject matter hereof and supersedes all proposals, oral or written, and all other prior communications between the PARTIES with respect to such subject matter, including, without limitation, that certain Confidential Disclosure Agreement by and between PFIZER and AXSOME with effective date of June 28, 2019 (“CDA”), which is hereby terminated and of no further force and effect. The PARTIES acknowledge and

agree that, as of the EFFECTIVE DATE, all CONFIDENTIAL INFORMATION (as defined in the CDA) disclosed by PFIZER or its AFFILIATES pursuant to the CDA shall be considered PFIZER's CONFIDENTIAL INFORMATION and subject to the terms set forth in this AGREEMENT.

18.11.2 In the event of any conflict between a material provision of this AGREEMENT and any Schedule hereto, the AGREEMENT shall control.

18.12 Counterparts. This Agreement may be executed in two or more counterparts, including electronic counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

18.13 Cumulative Remedies. No remedy referred to in this AGREEMENT is intended to be exclusive, but each shall be cumulative and in addition to any other remedy referred to in this AGREEMENT or otherwise available under law.

18.14 Waiver of Rule of Construction. Each PARTY has had the opportunity to consult with counsel in connection with the review, drafting and negotiation of this AGREEMENT. Accordingly, any rule of construction that any ambiguity in this AGREEMENT shall be construed against the drafting Party shall not apply.

**[Signature page to follow]**

IN WITNESS WHEREOF, the Parties intending to be bound have caused this Agreement to be executed by their duly authorized representatives as of the Effective Date.

**AXSOME THERAPEUTICS, INC.**

By: /s/ Herriot Tabuteau, M.D.  
Name: Herriot Tabuteau, M.D.  
Title: Chief Executive Officer

**PFIZER INC.**

By: /s/ Douglas Giordano  
Name: Douglas Giordano  
Title: Senior Vice President

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**Schedule 1.40**

Licensed Patent Rights

**Active Cases:**

Docket No.	Country	Application Date	App. No.	Patent No.	Status
***	***	***	***	***	***
***	***	***	***	***	***

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**Schedule 1.46**

Net Sales of Combination Products

[\*\*\*]

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**Schedule 1.79**

Share Transfer Agreement



**Schedule 1.92**

Transfer Schedule

[\*\*\*]

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**Schedule 5.1**

Equity Payment

The value of the SHARES shall be of [\*\*\*].

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**Schedule 5.2**

Upfront Payment

The UPFRONT PAYMENT shall be [\*\*\*].

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**Schedule 5.3**

Regulatory Approval Milestone Payments

<b>REGULATORY APPROVAL MILESTONE</b>	<b>REGULATORY APPROVAL MILESTONE PAYMENT</b>
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

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**Schedule 5.4**

Sales Milestone Payments

SALES MILESTONE		SALES MILESTONE PAYMENT
SALES MILESTONE 1	[***]	[***]
SALES MILESTONE 2	[***]	[***]
SALES MILESTONE 3	[***]	[***]
SALES MILESTONE 4	[***]	[***]

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**Schedule 5.5**

Royalty Payments

<b>MARGINAL SALES RANGE*</b>	<b>MARGINAL ROYALTY RATE</b>
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

\* For each PRODUCT, ranges are of the NET SALES in a CALENDAR YEAR of the PRODUCT that are made during the ROYALTY TERM.

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**Schedule 15.2**

Initial Press Release



**Schedule 16.2**  
Certificates of Insurance

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**Axsome Therapeutics, Inc.**

**Stock Unit Notice**  
**under the**  
**Axsome Therapeutics, Inc.**  
**2015 Omnibus Incentive Compensation Plan**

**Name of Grantee:** \_\_\_\_\_

This Notice evidences the award of restricted Stock Units (each, an "**RSU**," and collectively, the "**RSUs**") of Axsome Therapeutics, Inc., a Delaware corporation (the "**Company**"), that have been granted to you pursuant to the Axsome Therapeutics, Inc. 2015 Omnibus Incentive Compensation Plan (the "**Plan**") and conditioned upon your agreement to the terms of the attached Stock Unit Agreement (the "**Agreement**"). This Notice constitutes part of and is subject to the terms and provisions of the Agreement and the Plan, which are incorporated by reference herein. Each RSU is equivalent in value to one share of the Company Stock and represents the Company's commitment to issue one share of Company Stock at a future date, subject to the terms of the Agreement and the Plan. The RSUs are credited to a separate account maintained for you on the books and records of the Company (the "**Account**"). All amounts credited to the Account will continue for all purposes to be part of the general assets of the Company.

Grant Date: \_\_\_\_\_

Number of RSUs:

Vesting Schedule: All of the RSUs are nonvested and forfeitable as of the Grant Date. So long as your employment or service is continuous from the Grant Date through the applicable date upon which vesting is scheduled to occur:

twenty-five percent (25%) of the RSUs will be exercisable on the first anniversary of the Grant Date (the "Initial Vesting Date") and as to an additional twenty-five percent (25%) of the original number of RSUs at the end of each successive full twelve (12) month period following the Initial Vesting Date such that 100% of the RSUs will be vested and nonforfeitable on the fourth anniversary of the Grant Date.

Notwithstanding the foregoing, if your employment or service with the Company is terminated coincident with or within one year following a Change of Control by the Company or its successor without Cause, the RSUs that are unvested as of the date of termination will immediately become 100% exercisable.

\_\_\_\_\_  
Axsome Therapeutics, Inc.

\_\_\_\_\_  
Date

I acknowledge that I have carefully read the Agreement and the prospectus for the Plan. I agree to be bound by all of the provisions set forth in those documents. I also consent to electronic delivery of all notices or other information with respect to the RSUs or the Company.

\_\_\_\_\_  
Signature of Grantee

\_\_\_\_\_  
Date

**Axsome Therapeutics, Inc.**

**Stock Unit Agreement  
under the  
Axsome Therapeutics, Inc.  
2015 Omnibus Incentive Compensation Plan**

1. Terminology. Unless otherwise provided in this Agreement, capitalized terms used herein are defined in the Glossary at the end of this Agreement.

2. Vesting. All of the RSUs are nonvested and forfeitable as of the Grant Date. So long as your service or employment is continuous from the Grant Date through the applicable date upon which vesting is scheduled to occur, the RSUs will become vested and nonforfeitable in accordance with the vesting schedule set forth in the Notice. Except for the circumstances, if any, described in the Notice, none of the RSUs will become vested and nonforfeitable after your service or employment ceases.

3. Termination of Employment or Service. Unless otherwise provided in the Notice, if your service or employment with the Company ceases for any reason, all RSUs that are not then vested and nonforfeitable will be forfeited to the Company immediately and automatically upon such cessation without payment of any consideration therefor and you will have no further right, title or interest in or to such RSUs or the underlying shares of Company Stock.

4. Restrictions on Transfer. Neither this Agreement nor any of the RSUs may be assigned, transferred, pledged, hypothecated or disposed of in any way, whether by operation of law or otherwise, and the RSUs shall not be subject to execution, attachment or similar process. All rights with respect to this Agreement and the RSUs shall be exercisable during your lifetime only by you or your guardian or legal representative. Notwithstanding the foregoing, the RSUs may be transferred upon your death by last will and testament or under the laws of descent and distribution.

5. Settlement of RSUs.

(a) Manner of Settlement. You are not required to make any monetary payment (other than applicable tax withholding, if required) as a condition to settlement of the RSUs. The Company will issue to you, in settlement of your RSUs and subject to the provisions of Section 6 below, the number of whole shares of Company Stock that equals the number of whole RSUs that become vested, and such vested RSUs will terminate and cease to be outstanding upon such issuance of the shares. Upon issuance of such shares, the Company will determine the form of delivery (e.g., a stock certificate or electronic entry evidencing such shares) and may deliver such shares on your behalf electronically to the Company's designated stock plan administrator or such other broker-dealer as the Company may choose at its sole discretion, within reason.

(b) Timing of Settlement. Your RSUs will be settled by the Company, via the issuance of Company Stock as described herein, on the date that the RSUs become vested and nonforfeitable<sup>1</sup>. However, if a scheduled issuance date falls on a Saturday, Sunday or federal holiday, such issuance date shall instead fall on the next following day that the principal executive offices of the Company are open for business. In all cases, the issuance and delivery of shares under this Agreement is intended to comply with Treasury Regulation 1.409A-1(b)(4) and shall be construed and administered in such a manner.

6. Tax Withholding. On or before the time you receive a distribution of the shares subject to your RSUs, or at any time thereafter as requested by the Company, you hereby authorize any required withholding from the Company Stock issuable to you and/or otherwise agree to make adequate provision in cash for any sums required to satisfy the federal, state, local and foreign tax withholding obligations of the Company or any Affiliate which arise in connection with your RSUs (the "**Withholding Taxes**").

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<sup>1</sup>NTD: For executive officers and non-employee directors, this provision may be revised to provide for deferred settlement in compliance with Section 409A of the Internal Revenue Code.

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Additionally, the Company may, in its sole discretion, satisfy all or any portion of the Withholding Taxes obligation relating to your RSUs by any of the following means or by a combination of such means: (i) withholding from any compensation otherwise payable to you by the Company; (ii) causing you to tender a cash payment; (iii) permitting you to enter into a "same day sale" commitment with a broker-dealer that is a member of the Financial Industry Regulatory Authority (a "**FINRA Dealer**") whereby you irrevocably elect to sell a portion of the shares to be delivered under the Agreement to satisfy the Withholding Taxes and whereby the FINRA Dealer irrevocably commits to forward the proceeds necessary to satisfy the Withholding Taxes directly to the Company; or (iv) withholding shares of Company Stock from the shares of Company Stock issued or otherwise issuable to you in connection with the RSUs with a Fair Market Value (measured as of the date shares of Company Stock are issued to you pursuant to Section 5) equal to the amount of such Withholding Taxes; provided, however, that the number of such shares of Company Stock so withheld shall not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income. Unless the tax withholding obligations of the Company are satisfied, the Company shall have no obligation to deliver to you any Company Stock. In the event the Company's obligation to withhold arises prior to the delivery to you of Company Stock or it is determined after the delivery of Company Stock to you that the amount of the Company's withholding obligation was greater than the amount withheld by the Company, you agree to indemnify and hold the Company harmless from any failure by the Company to withhold the proper amount.

7. Adjustments for Corporate Transactions and Other Events.

(a) Stock Dividend, Stock Split and Reverse Stock Split. Upon a stock dividend of, or stock split or reverse stock split or other event described in Section 4(d) of the Plan affecting, the Company Stock, the number of outstanding RSUs shall, without further action of the Administrator, be adjusted to reflect such event; provided, however, that any fractional RSUs resulting from any such adjustment shall be eliminated. Adjustments under this paragraph will be made by the Administrator, whose determination as to what adjustments, if any, will be made and the extent thereof will be final, binding and conclusive.

(b) Merger, Consolidation and Other Events. If the Company shall be the surviving or resulting corporation in any merger or consolidation and the Company Stock shall be converted into other securities, the RSUs shall pertain to and apply to the securities to which a holder of the number of shares of Company Stock subject to the RSUs would have been entitled. If the stockholders of the Company receive by reason of any distribution in total or partial liquidation or pursuant to any merger of the Company or acquisition of its assets, securities of another entity or other property (including cash), then the rights of the Company under this Agreement shall inure to the benefit of the Company's successor, and this Agreement shall apply to the securities or other property (including cash) to which a holder of the number of shares of Company Stock subject to the RSUs would have been entitled, in the same manner and to the same extent as the RSUs.

8. Non-Guarantee of Employment or Service Relationship. Nothing in the Plan or this Agreement shall alter your at-will or other employment status or other service relationship with the Company, nor be construed as a contract of employment or service relationship between the Company and you, or as a contractual right of you to continue in the employ of, or in a service relationship with, the Company for any period of time, or as a limitation of the right of the Company to discharge you at any time with or without cause or notice and whether or not such discharge results in the forfeiture of any nonvested and forfeitable RSUs or any other adverse effect on your interests under the Plan.

9. Rights as Stockholder. You shall not have any of the rights of a stockholder with respect to any shares of Company Stock that may be issued in settlement of the RSUs until such shares of Company Stock have been issued to you.

10. The Company's Rights. The existence of the RSUs shall not affect in any way the right or power of the Company or its stockholders to make or authorize any or all adjustments, recapitalizations, reorganizations, or other changes in the Company's capital structure or its business, or any merger or consolidation of the Company, or any issue of bonds, debentures, preferred or other stocks with preference ahead of or convertible into, or otherwise affecting the Company Stock or the rights thereof, or the

dissolution or liquidation of the Company, or any sale or transfer of all or any part of the Company's assets or business, or any other corporate act or proceeding, whether of a similar character or otherwise.

11. Restrictions on Issuance of Shares. The issuance of shares of Company Stock upon settlement of the RSUs shall be subject to and in compliance with all applicable requirements of federal, state, or foreign law with respect to such securities. No shares of Company Stock may be issued hereunder if the issuance of such shares would constitute a violation of any applicable federal, state, or foreign securities laws or other law or regulations or the requirements of any stock exchange or market system upon which the Company Stock may then be listed. The inability of the Company to obtain from any regulatory body having jurisdiction the authority, if any, deemed by the Company's legal counsel to be necessary to the lawful issuance of any shares subject to the RSUs shall relieve the Company of any liability in respect of the failure to issue such shares as to which such requisite authority shall not have been obtained. As a condition to the settlement of the RSUs, the Company may require you to satisfy any qualifications that may be necessary or appropriate, to evidence compliance with any applicable law or regulation, and to make any representation or warranty with respect thereto as may be requested by the Company.

12. Notices. All notices and other communications made or given pursuant to this Agreement shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five (5) days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company, or in the case of notices delivered to the Company by you, addressed to the Administrator, care of the Company for the attention of its Secretary at its principal executive office or, in either case, if the receiving party consents in advance, transmitted and received via telecopy or via such other electronic transmission mechanism as may be available to the parties. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this award of RSUs by electronic means or to request your consent to participate in the Plan or accept this award of RSUs by electronic means. You hereby consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

13. Entire Agreement. This Agreement, together with the relevant Notice and the Plan, contains the entire agreement between the parties with respect to the RSUs granted hereunder. Any oral or written agreements, representations, warranties, written inducements, or other communications made prior to the execution of this Agreement with respect to the RSUs granted hereunder shall be void and ineffective for all purposes.

14. Amendment. This Agreement may be amended from time to time by the Administrator in its discretion; provided, however, that this Agreement may not be modified in any manner that would have a materially adverse effect on the RSUs as determined in the discretion of the Administrator, except as provided in the Plan or in a written document signed by each of the parties hereto.

15. Recoupment Policy. You agree that, subject to the requirements of applicable law, if you breach any restrictive covenant agreement between you and the Company or you otherwise engage in activities that constitute Cause either while employed by, or providing service to, the Company or within two years thereafter, the RSU shall terminate, and the Company may rescind any delivery of shares upon vesting or settlement, as applicable on such terms as the Committee shall determine, including the right to require that in the event of any such rescission, (a) you shall return to the Company the shares received upon settlement of the RSU or, (b) if you no longer owns the shares, you shall pay to the Company the amount of any gain realized or payment received as a result of any sale or other disposition of the shares (or, in the event you transfer the shares by gift or otherwise without consideration, the Fair Market Value of the shares on the date of the breach of any restrictive covenant agreement or activity constituting Cause). You agree that payment shall be made in such manner and on such terms and conditions as may be required by the Committee and you shall be entitled to set off against the amount of any such payment any amounts otherwise owed to you by the Company. In addition, you agree that the RSU shall be subject to any applicable clawback or recoupment policies, share trading policies and other policies that may be implemented by the Board from time to time.

409A Savings Clause. This Agreement and the RSUs granted hereunder are intended to either fit within the "short-term deferral" exemption from Section 409A of the Code as set forth in Treasury Regulation Section 1.409A-1(b)(4) or comply with Section 409A. Notwithstanding the foregoing, if it is determined that the RSUs fail to satisfy the requirements of the short-term deferral rule and are otherwise deferred compensation subject to Section 409A, and if you are a "Specified Employee" (within the meaning set forth Section 409A(a)(2)(B)(i) of the Code) as of the date of your separation from service (within the meaning of Treasury Regulation Section 1.409A-1(h)), then the issuance of any shares that would otherwise be made upon the date of the separation from service or within the first six (6) months thereafter will not be made on the originally scheduled date(s) and will instead be issued in a lump sum on the date that is six (6) months and one day after the date of the separation from service, but if and only if such delay in the issuance of the shares is necessary to avoid the imposition of additional taxation on you in respect of the shares under Section 409A of the Code. Each installment of shares that vests is intended to constitute a "separate payment" for purposes of Section 409A of the Code and Treasury Regulation Section 1.409A-2(b)(2).

16. No Obligation to Minimize Taxes. The Company has no duty or obligation to minimize the tax consequences to you of this award of RSUs and shall not be liable to you for any adverse tax consequences to you arising in connection with this award. You are hereby advised to consult with your own personal tax, financial and/or legal advisors regarding the tax consequences of this award and by signing the Notice, you have agreed that you have done so or knowingly and voluntarily declined to do so.

17. Conformity with Plan. This Agreement is intended to conform in all respects with, and is subject to all applicable provisions of, the Plan. Inconsistencies between this Agreement and the Plan shall be resolved in accordance with the terms of the Plan. In the event of any ambiguity in this Agreement or any matters as to which this Agreement is silent, the Plan shall govern. A copy of the Plan is available upon request to the Administrator.

18. No Funding. This Agreement constitutes an unfunded and unsecured promise by the Company to issue shares of Company Stock in the future in accordance with its terms. You have the status of a general unsecured creditor of the Company as a result of receiving the grant of RSUs.

19. Effect on Other Employee Benefit Plans. The value of the RSUs subject to this Agreement shall not be included as compensation, earnings, salaries, or other similar terms used when calculating your benefits under any employee benefit plan sponsored by the Company, except as such plan otherwise expressly provides. The Company expressly reserves its rights to amend, modify, or terminate any of the Company's employee benefit plans.

20. Governing Law. The validity, construction and effect of this Agreement, and of any determinations or decisions made by the Administrator relating to this Agreement, and the rights of any and all persons having or claiming to have any interest under this Agreement, shall be determined exclusively in accordance with the laws of the State of Delaware, without regard to its provisions concerning the applicability of laws of other jurisdictions. As a condition of this Agreement, you agree that you will not bring any action arising under, as a result of, pursuant to or relating to, this Agreement in any court other than a federal or state court in the districts which include Delaware, and you hereby agree and submit to the personal jurisdiction of any federal court located in the district which includes Delaware or any state court in the district which includes Delaware. You further agree that you will not deny or attempt to defeat such personal jurisdiction or object to venue by motion or other request for leave from any such court.

21. Resolution of Disputes. Any dispute or disagreement which shall arise under, or as a result of, or pursuant to or relating to, this Agreement shall be determined by the Administrator in good faith in its absolute and uncontrolled discretion, and any such determination or any other determination by the Administrator under or pursuant to this Agreement and any interpretation by the Administrator of the terms of this Agreement, will be final, binding and conclusive on all persons affected thereby. You agree that before you may bring any legal action arising under, as a result of, pursuant to or relating to, this Agreement you will first exhaust your administrative remedies before the Administrator. You further agree that in the event that the Administrator does not resolve any dispute or disagreement arising under, as a result of, pursuant to or relating to, this Agreement to your satisfaction, no legal action may be commenced or maintained relating to this Agreement more than twenty-four (24) months after the Administrator's decision.

22. Headings. The headings in this Agreement are for reference purposes only and shall not affect the meaning or interpretation of this Agreement.

23. Electronic Delivery of Documents. By your signing the Notice, you (i) consent to the electronic delivery of this Agreement, all information with respect to the Plan and the RSUs, and any reports of the Company provided generally to the Company's stockholders; (ii) acknowledge that you may receive from the Company a paper copy of any documents delivered electronically at no cost to you by contacting the Company by telephone or in writing; (iii) further acknowledge that you may revoke your consent to the electronic delivery of documents at any time by notifying the Company of such revoked consent by telephone, postal service or electronic mail; and (iv) further acknowledge that you understand that you are not required to consent to electronic delivery of documents.

24. No Future Entitlement. By your signing the Notice, you acknowledge and agree that: (i) the grant of a restricted stock unit award is a one-time benefit which does not create any contractual or other right to receive future grants of restricted stock units, or compensation in lieu of restricted stock units, even if restricted stock units have been granted repeatedly in the past; (ii) all determinations with respect to any such future grants and the terms thereof will be at the sole discretion of the Committee; (iii) the value of the restricted stock units is an extraordinary item of compensation which is outside the scope of your employment contract, if any; (iv) the value of the restricted stock units is not part of normal or expected compensation or salary for any purpose, including, but not limited to, calculating any termination, severance, resignation, redundancy, end of service payments or similar payments, or bonuses, long-service awards, pension or retirement benefits; (v) the vesting of the restricted stock units ceases upon termination of Service with the Company or transfer of employment from the Company, or other cessation of eligibility for any reason, except as may otherwise be explicitly provided in this Agreement; (vi) the Company does not guarantee any future value of the restricted stock units; and (vii) no claim or entitlement to compensation or damages arises if the restricted stock units decrease or do not increase in value and you irrevocably release the Company from any such claim that does arise.

25. Personal Data. For purposes of the implementation, administration and management of the restricted stock units or the effectuation of any acquisition, equity or debt financing, joint venture, merger, reorganization, consolidation, recapitalization, business combination, liquidation, dissolution, share exchange, sale of stock, sale of material assets or other similar corporate transaction involving the Company (a "**Corporate Transaction**"), you consent, by execution of the Notice, to the collection, receipt, use, retention and transfer, in electronic or other form, of your personal data by and among the Company and its third party vendors or any potential party to a potential Corporate Transaction. You understand that personal data (including but not limited to, name, home address, telephone number, employee number, employment status, social security number, tax identification number, date of birth, nationality, job and payroll location, data for tax withholding purposes and shares awarded, cancelled, vested and unvested) may be transferred to third parties assisting in the implementation, administration and management of the restricted stock units or the effectuation of a Corporate Transaction and you expressly authorize such transfer as well as the retention, use, and the subsequent transfer of the data by the recipient(s). You understand that these recipients may be located in your country or elsewhere, and that the recipient's country may have different data privacy laws and protections than your country. You understand that data will be held only as long as is necessary to implement, administer and manage the restricted stock units or effect a Corporate Transaction. You understand that you may, at any time, request a list with the names and addresses of any potential recipients of the personal data, view data, request additional information about the storage and processing of data, require any necessary amendments to data or refuse or withdraw the consents herein, in any case without cost, by contacting in writing the Company's Secretary. You understand, however, that refusing or withdrawing your consent may affect your ability to accept a restricted stock unit award.

*{Glossary begins on next page}*

## GLOSSARY

(a)“ **Administrator**” means the Committee as defined in the Plan.

(b)“ **Agreement**” means this document, as amended from time to time, together with the Plan which is incorporated herein by reference.

(c) “**Cause**” has the meaning set forth in the Plan.

(d) “**Change of Control**” shall have the meaning set forth in the Plan.

(e)“ **Code**” means the Internal Revenue Code of 1986, as amended, and the Treasury regulations and other guidance promulgated thereunder.

(f)“ **Company Stock**” shall mean common stock of the Company.

(g)“ **Company**” means Axsome Therapeutics, Inc., and shall include all its successors except where the context otherwise requires. For purposes of determining whether a Change of Control has occurred, Company shall mean only Axsome Therapeutics, Inc.

(h)“ **Fair Market Value**” has the meaning set forth in the Plan.

(i)“ **Grant Date**” means the effective date of a grant of RSUs made to you as set forth in the relevant Notice.

(j)“ **Notice**” means the statement, letter or other written notification provided to you by the Company setting forth the terms of a grant of RSUs made to you.

(k)“ **Plan**” means the Axsome Therapeutics, Inc. 2015 Omnibus Incentive Compensation Plan, as in effect from time to time.

(l)“ **RSU**” means the Company’s commitment to issue one share of Company Stock at a future date, subject to the terms of the Agreement and the Plan.

(m)“ **You**” or “**Your**” means the recipient of the RSUs as reflected on the applicable Notice. Whenever the word “you” or “your” is used in any provision of this Agreement under circumstances where the provision should logically be construed, as determined by the Administrator, to apply to the estate, personal representative, or beneficiary to whom the RSUs may be transferred by will or by the laws of descent and distribution, the words “you” and “your” shall be deemed to include such person.

{End of Agreement}

**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. 333-230296) 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-3ASR No. 333-235372) of Axsome Therapeutics, Inc. and in the related Prospectus;

of our report dated March 12, 2020, 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, 2019.

/s/ Ernst & Young LLP

New York, NY  
March 12, 2020

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**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 12, 2020

/s/ Herriot Tabuteau, M.D.  
Herriot Tabuteau, M.D.  
Chief Executive Officer  
(Principal Executive Officer)

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**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 12, 2020

/s/ Nick Pizzie  
Nick Pizzie  
Chief Financial Officer  
(Principal Financial and Accounting Officer)

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**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, 2019 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 12, 2020

/s/ Herriot Tabuteau, M.D.  
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Herriot Tabuteau, M.D.  
Chief Executive Officer  
(Principal Executive Officer)

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**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, 2019 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 12, 2020

/s/ Nick Pizzie  
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Nick Pizzie  
Chief Financial Officer  
(Principal Financial and Accounting Officer)

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