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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, 2017

OR

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

For the transition period from _____ to _____

Commission File Number 001-37635

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

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

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

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

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

Securities registered pursuant to Section 12(g) of the Act:
None

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

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

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

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

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

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

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

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

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

The aggregate market value of voting common stock held by non-affiliates of the registrant (assuming for purposes of this calculation, without conceding, that all executive officers and directors are "affiliates") was approximately $85.5 million as of June 30, 2017, based on the closing sale price of such stock as reported on the Nasdaq Global Market.

There were 25,492,992 shares of the registrant's common stock outstanding as of March 2, 2018.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2018 Annual Meeting of Stockholders (the "Proxy Statement"), to be filed within 120 days of the registrant's fiscal year ended December 31, 2017, 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, 2017

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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 product candidate portfolio includes five CNS product candidates, AXS-05, AXS-09, AXS-02, AXS-07, and AXS-06 which we are developing for multiple indications. We are conducting a Phase 3 trial with AXS-05 in treatment resistant depression, or TRD, which we refer to as the STRIDE-1 study, and a Phase 2/3 trial in agitation associated with Alzheimer's disease, or AD, which we refer to as the ADVANCE-1 study. Additionally, AXS-05 is being developed for smoking cessation. AXS-09 is being developed for CNS disorders. We are also conducting a Phase 3 trial with AXS-02 in knee osteoarthritis, or OA, associated with bone marrow lesions, or BMLs, pursuant to a Special Protocol Assessment, or SPA, which we refer to as the COAST-1 study. We also plan to initiate a Phase 3 trial with AXS-02 in chronic low back pain, or CLBP, associated with Modic changes, or MCs. AXS-07 is initially being developed for the acute treatment of migraine. Lastly, AXS-06 is being developed for the treatment of osteoarthritis and rheumatoid arthritis and for the reduction of the risk of nonsteroidal anti-inflammatory drug, or NSAID, associated gastric ulcers. Additionally, we are currently evaluating other preclinical product candidates, which we intend to develop for CNS disorders. We aim to become a fully integrated biopharmaceutical company that develops and commercializes differentiated therapies that expand the treatment options available to caregivers and improve the lives of patients living with CNS disorders.

AXS-05, is an innovative oral fixed-dose combination of dextromethorphan, or DM, and bupropion. We are developing AXS-05 initially for the following three indications: TRD, agitation associated with AD, and as an aid to smoking cessation. DM is active at multiple CNS receptors but is rapidly and extensively metabolized in humans. As a result, it is difficult to attain potential therapeutic plasma levels of DM when it is dosed as a single agent. AXS-05 uses bupropion as a novel drug delivery method to inhibit DM metabolism and increase its bioavailability. We have demonstrated in three Phase 1 trials that DM plasma levels are substantially increased into a potentially therapeutic range with the co-administration of bupropion. Bupropion is itself active at distinct CNS receptors providing the potential for an additive or synergistic effect. We intend to seek U.S. Food and Drug Administration, or FDA ,approval for AXS-05 utilizing the 505(b)(2) regulatory development pathway.

AXS-09 is a novel, oral medicine combination 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 our 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. The increased DM concentrations with AXS-09 are comparabale to those achieved with AXS-05. 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-02, disodium zoledronate tetrahydrate, is a potentially first-in-class, oral, targeted, non-opioid therapeutic for chronic pain. AXS-02 is a potent inhibitor of osteoclasts, which are bone remodeling cells that break down bone tissue. We are initially developing AXS-02 for the treatment of pain in the following two conditions: knee OA associated with BMLs and CLBP associated with type 1 or mixed type 1 and type 2 MCs. These conditions exhibit target lesions or specific pathology that we believe may be addressed by the mechanisms of action of AXS-02, such as inhibition of osteoclast activity. These mechanisms may result in a reduction of pain in these conditions. We have successfully completed a Phase 1 trial of AXS-02 to characterize the pharmacokinetics of zoledronic acid and its effects on markers of bone resorption after oral administration of AXS-02. The results of our Phase 1 trial demonstrated that oral

administration of AXS-02 tablets resulted in rapid absorption of zoledronic acid, which is the active molecule in AXS-02 and the free acid form of disodium zoledronate tetrahydrate, and substantial suppression of bone resorption markers, which are proteins indicative of bone tissue breakdown. We intend to seek FDA approval for AXS-02 utilizing the 505(b)(2) regulatory development pathway.

AXS-07, is a novel, oral, fixed-dose combination 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-HT1B/D agonist that inhibits calcitonin gene-related peptide (CGRP)-mediated vasodilation, has been shown to have central trigeminal antinociceptive activity, and may reduce the release of inflammatory mediators from trigeminal nerves. Rizatriptan is approved as a single agent for the acute treatment of migraine. We intend to seek FDA approval for AXS-07 utilizing the 505(b)(2) regulatory development pathway.

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

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

Our Strategy

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

- ***Pursue novel CNS indications with high unmet medical need.*** We believe that CNS disorders are significantly underserved therapeutic segments with currently limited treatment options. We are initially developing our product candidates for indications that have no or few FDA-approved pharmacological treatments. For example, there currently is no drug approved by the FDA or the EMA for agitation associated with Alzheimer's disease, the pain of knee OA associated with BMLs, or CLBP associated with MCs. There is currently only one FDA-approved drug 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 of approved treatments, should provide us with attractive commercial opportunities.

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

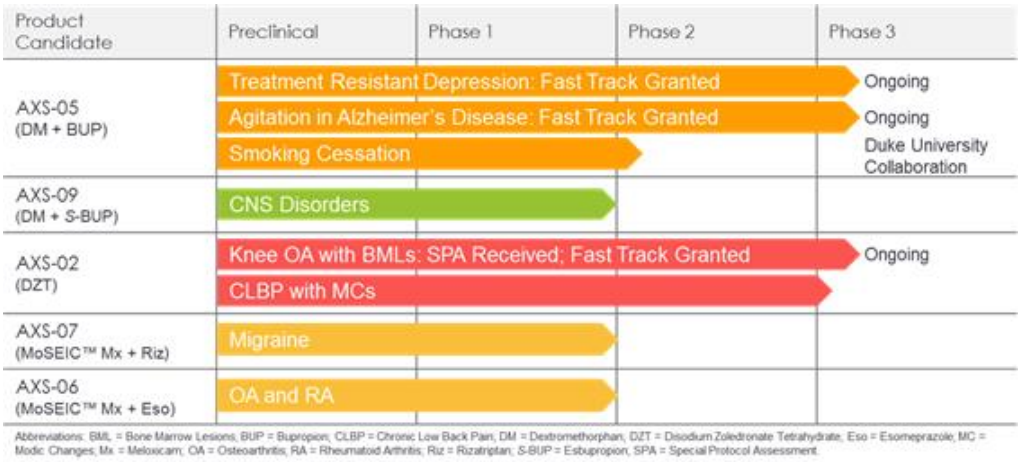
- ***Develop products with differentiated profiles.*** We aim to develop products with novel mechanisms of action for the intended indications that may yield differentiated product profiles. For example, AXS-05 and AXS-09 combine several mechanisms of action resulting in a unique pharmacological profile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

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

- ***Reduce clinical and regulatory risk, limit development costs, and accelerate time to market.*** Our product candidates incorporate chemical entities with long histories of clinical use and well-characterized safety profiles. Use of well-characterized molecules has allowed us to rapidly complete early clinical development of our product candidates, and may reduce the risk of late-stage clinical failures due to unexpected toxicities. This strategy also allows us to seek FDA approval for 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 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 product candidate pipeline is summarized in the table below:



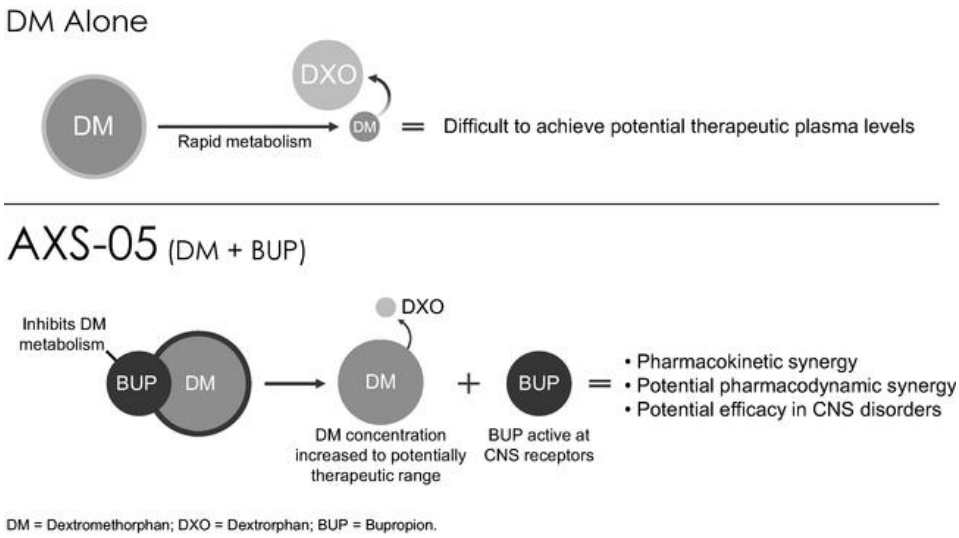
AXS-05

Overview

AXS-05 is an innovative oral fixed-dose combination of dextromethorphan and bupropion under development for the treatment of CNS disorders. DM is active at multiple CNS receptors but is rapidly metabolized into dextrorphan, or DXO, when dosed alone. Our combination uses bupropion as a novel drug delivery method to inhibit DM metabolism and increase its bioavailability. Bupropion itself is also active at distinct CNS receptors. The activity of the two components may provide an additive or synergistic effect.

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

Scientific Rationale



DM = Dextromethorphan; DXO = Dextrorphan; BUP = Bupropion.

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, as shown in the figure above, 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. We have demonstrated in three Phase 1 trials that co-administration of bupropion and DM leads to substantially increased DM plasma levels. This positive pharmacokinetic interaction between bupropion and DM therefore may enable DM's clinical utility by increasing DM's plasma levels into a potentially therapeutic range. We believe this dual pharmacodynamic and pharmacokinetic synergy results in a unique pharmacological profile that could potentially be efficacious in CNS disorders.

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

DM is a noncompetitive N-methyl-D-aspartate, or NMDA, receptor antagonist, a sigma-1 receptor agonist, and an inhibitor of the serotonin transporter, or SERT, and norepinephrine transporter, or NET. Each of these mechanisms of action has been shown to be associated with antidepressant response. DM is a well-known agent that is used as an ingredient in over-the-counter cough and cold preparations. DM, in combination with quinidine, was approved by the FDA in 2010 for the treatment of pseudobulbar affect, also known as emotional lability. Like bupropion in our product candidate, quinidine is used to inhibit the metabolism of DM and increase its plasma concentrations. Unlike bupropion, however, the quinidine in the preparation does not have CNS activity.

Treatment Resistant Depression (TRD)

We are developing AXS-05 for the treatment of TRD. Currently only one product, Symbyax, a combination of olanzapine and fluoxetine, which is marketed by Eli Lilly and Company, is approved in the United States for the treatment of TRD.

Indication Overview

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 Institute of Health, or NIH, an estimated 6.7% of U.S. adults experience MDD each year, while 3.3% of individuals 13 to 18 years of age experience a seriously debilitating depressive disorder. Results of the Sequenced Treatment Alternatives to Relieve Depression, or STAR*D trial, funded by the National Institute of Mental Health, indicate that nearly two-thirds of diagnosed and treated patients do not experience adequate treatment response with first-line therapy, and that the majority of these initial failures also fail second-line treatment. Based on these observations, we estimate that there are approximately 3 million patients with TRD in the United States.

Rationale for the Use of AXS-05 in TRD

The rationale for the use of AXS-05 in TRD is based on the mechanisms of action of DM, preclinical evidence of antidepressant effects of DM, preliminary clinical evidence of antidepressant effects of DM when co-administered with an inhibitor of its metabolism, and the established clinical efficacy of bupropion in MDD.

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

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

Clinical Rationale. Administration of DM with an inhibitor of its metabolism has been shown to reduce depressive symptoms, measured using the Beck Depression Inventory Second Edition, or BDI-II, in a third-party study. In a 326-patient, randomized, double-blind, placebo-controlled trial in patients with pseudobulbar affect, co-administration of DM and the metabolic inhibitor quinidine resulted in a statistically significant reduction in depressive symptoms as compared to placebo at the 30 mg DM / 10 mg quinidine dose at 12 weeks, as shown in the figure below. Patients were excluded from the study if their BDI-II score was greater than 19, with a score in the range of 0 to 13 corresponding to minimal depression and 14 to 19 corresponding to mild depression. Assessment of depressive symptoms was a pre-specified secondary endpoint in this trial.

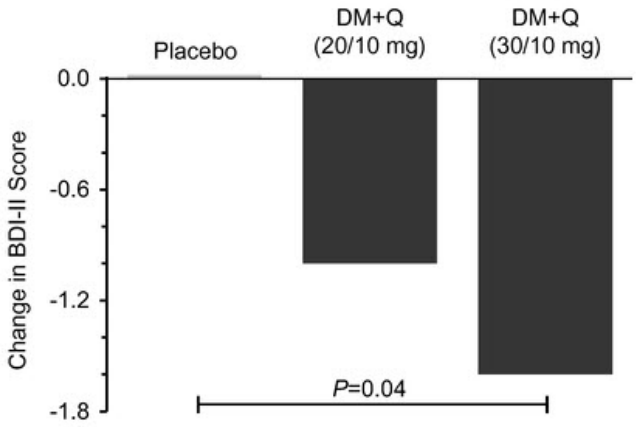
Additionally, administration of DM with an inhibitor of its metabolism has also been shown to reduce depressive symptoms, measured using the Cornell Scale for Depression in Dementia, or CSDD, in a third-party study. In a randomized, double-blind, placebo-controlled, two stage trial in 220 patients with probable AD and clinically

meaningful agitation, co-administration of DM and the metabolic inhibitor quinidine resulted in a statistically significant reduction in depressive symptoms as compared to placebo at the 30 mg DM / 10 mg quinidine dose at 5 weeks, as shown in the figure below. Patients with severe depression were excluded from the study. Assessment of depressive symptoms was a pre-specified secondary endpoint in this trial. These studies potentially inform the assessment of DM for TRD.

Administration of DM with an inhibitor of its metabolism has been shown to reduce depressive symptoms, measured using the Montgomery Asberg Depression Rating Scale, or MADRS, in patients with TRD, in a third party study. In a 20-patient, open-label trial in patients with TRD, co-administration of DM and the metabolic inhibitor quinidine resulted in a 45% overall response rate in the intention to treat sample, with response defined as a 50% or greater decrease in MADRS score from baseline to primary outcome.

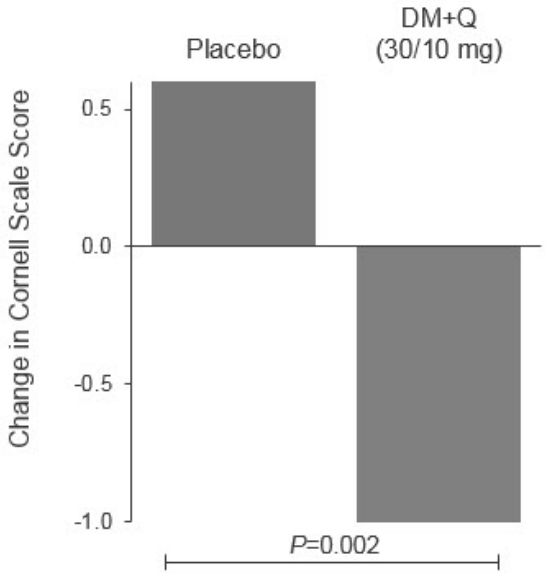
According to the FDA package insert for the combination of DM and quinidine (Nuedexta), DM is the pharmacologically active ingredient of the DM / quinidine combination that acts on the CNS, with quinidine serving to increase DM plasma levels. The plasma concentrations of DM, measured using AUC_{0-12}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

Depressive symptom change with DM and metabolic inhibitor quinidine (Q) in patients with pseudobulbar affect at 12 weeks



Source: *Pioro EP, et al. Ann Neurol 2010;68:693-702.*

Depressive symptom change with DM and metabolic inhibitor quinidine (Q) in patients with agitation in Alzheimer's disease at 5 weeks



Source: *Cummings J, et al. JAMA. 2015;314:1242-1254.*

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 as many as 40% of patients. Agitation is characterized by emotional distress, aggressive behaviors, disruptive irritability, and disinhibition. Agitation associated with AD has been associated with increased caregiver burden, decreased functioning, earlier nursing home placement, and death.

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

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

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

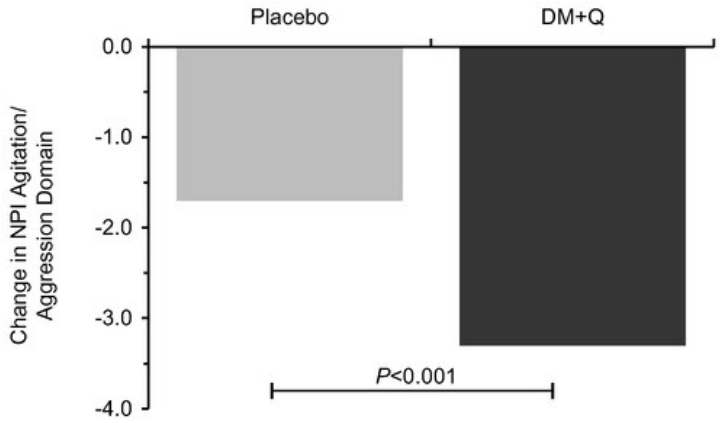
Mechanistic rationale. Mechanisms of action of DM include NMDA receptor antagonism and sigma-1 receptor agonism. Altered glutamate transmission via NMDA receptors has been suggested to play a role in behavioral changes in dementia, and clinical evidence suggests that NMDA antagonism may reduce agitation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

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

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

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

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



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

Smoking Cessation

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

Indication Overview

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

Rationale for the Development of AXS-05 in Smoking Cessation

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

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

of AXS-05 combined with their positive pharmacokinetic interaction supports the potential for AXS-05 to be effective in the treatment of tobacco dependence in humans.

Clinical Development of AXS-05

We are developing AXS-05 and intend to seek FDA approval for the product utilizing the 505(b)(2) regulatory pathway. Section 505(b)(2) of the FDCA permits an applicant to file an NDA that relies, in part, on data not developed by or for the applicant and to which the applicant has not received a right of reference, such as the FDA's findings of safety and efficacy in the approval of a similar drug, or reference listed drug, or published literature, in support of its application. We have completed three Phase 1 pharmacokinetic clinical trials of AXS-05 under clinical trial applications with Health Canada. In each study, administration of bupropion in combination with DM resulted in a substantial increase in DM plasma concentrations measured using C_{max} and AUC at all doses tested.

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.

Completed Phase 1 Trials of AXS-05

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

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

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

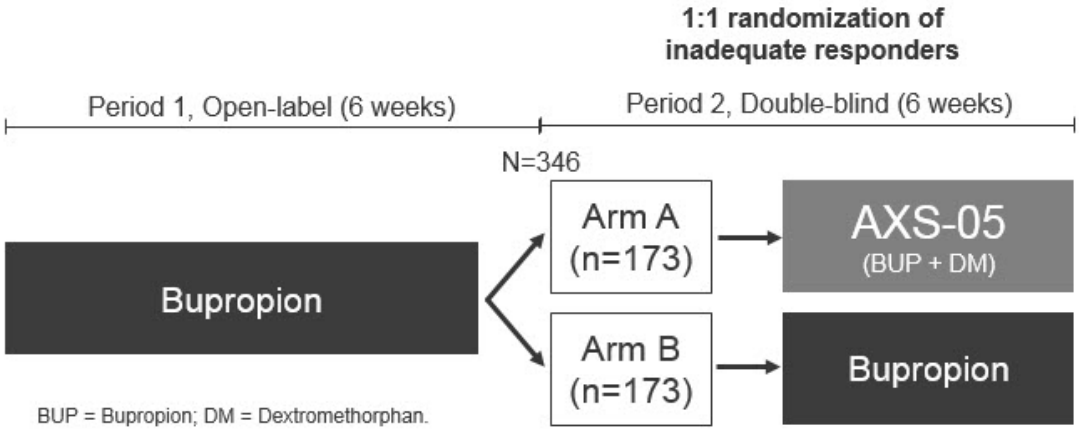
The second Phase 1 trial was a randomized, multiple-dose, open-label study to determine the pharmacokinetics of DM when various doses of DM are administered concomitantly with various doses of bupropion and to assess safety during co-administration of bupropion and DM. A total of 40 healthy, adult volunteers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

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

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

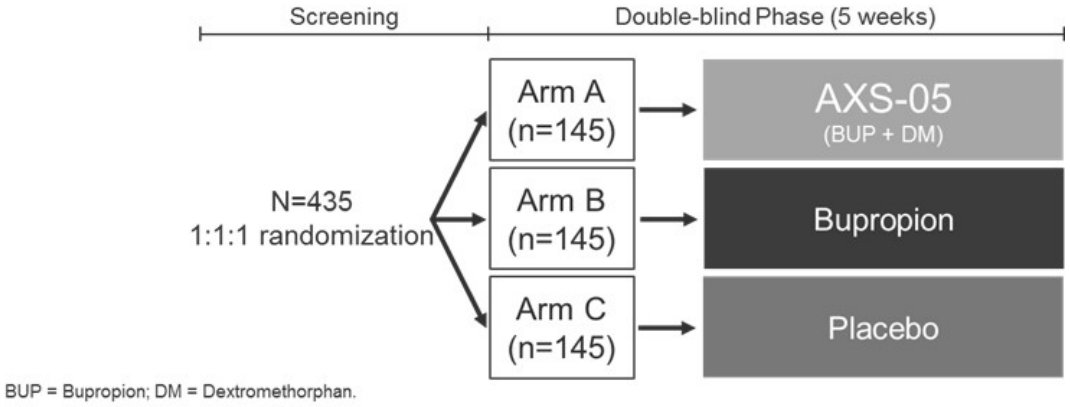
Ongoing STRIDE-1 Study

In March 2016, we initiated the STRIDE-1 study, a Phase 3, randomized, double-blind, active-controlled trial to assess the efficacy and safety of AXS-05 in the treatment of TRD. Patients with MDD who have had inadequate response to one or two antidepressant treatments are treated in an open-label fashion with bupropion during a 6-week lead-in period. Patients who had inadequate response to bupropion during this lead-in period are considered to have TRD and are randomly assigned in a 1:1 ratio to receive bupropion or AXS-05 under fasting conditions in a double-blind fashion for 6 weeks. The primary endpoint is the change in the MADRS after 6 weeks of treatment. The trial will enroll a total of approximately 346 randomized patients. Two interim analyses are planned. The first interim analysis will be performed on the first approximately 40% of the target number of subjects to assess futility. The second interim analysis will be performed on the first approximately 60% of the target number of subjects to assess efficacy.



Ongoing ADVANCE-1 Study

In July 2017, we initiated the ADVANCE-1 study, a Phase 2/3, randomized, double-blind, controlled trial to evaluate the efficacy and safety of AXS-05 in patients with agitation associated with AD. Patients with probable AD and clinically significant agitation are randomly assigned in a 1:1:1 ratio to receive bupropion, placebo, or AXS-05 in a double-blind fashion. The primary endpoint is the change in the Cohen-Mansfield Agitation Inventory. The trial will randomize a total of approximately 435 patients. Two interim analyses are planned. The first interim analysis will be performed on the first approximately 30% of the target number of subjects to assess futility. The second interim analysis will be performed on the first approximately 60% of the target number of subjects to assess efficacy.



AXS-09

AXS-09 is a novel, oral medicine consisting of chirally pure esbupropion and DM under development for the treatment of CNS disorders. 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-02

Overview

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

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

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

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

Novel Mechanisms of Action for Pain

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

Targeted Therapy for Pain

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

Orally Administered

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

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

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

Infrequent Dosing and Convenient Regimen

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

Extended Pain Relief

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

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

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

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

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

We are developing AXS-02 for the treatment of the pain of knee OA associated with BMLs. There is currently no therapy specifically approved by the FDA or the EMA to treat this subset of knee OA. The FDA has agreed to an

SPA for our ongoing Phase 3 COAST-1 study in subjects with knee OA and BMLs. The FDA has also granted Fast Track designation for AXS-02 for the treatment of the pain of knee OA associated with BMLs.

Indication Overview

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

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

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

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

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

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

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

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

Indication Overview

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

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

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

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

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

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

Clinical Development of AXS-02

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

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

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

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

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

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

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

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

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

Completed Phase 1 Trial of AXS-02

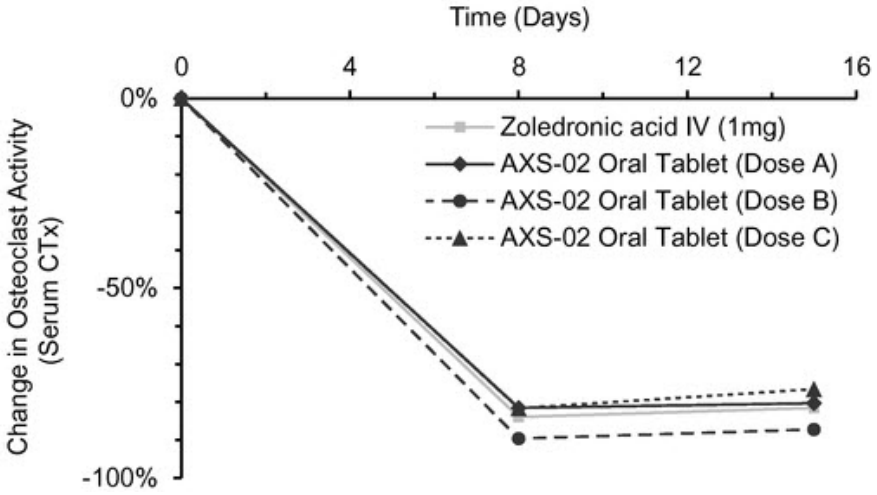
We conducted a Phase 1 trial to assess the fasting pharmacokinetics, pharmacodynamics, safety, and tolerability of orally administered AXS-02 tablets in healthy adult male and postmenopausal female volunteers under a Health Canada Clinical Trial Application. The trial was a randomized, open-label, partial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

Zoledronic acid was rapidly absorbed after oral administration of AXS-02 tablets with median time to reach the maximum plasma concentration, or T_{max}, of 30 to 45 minutes. The absolute oral bioavailability of zoledronic acid after administration of AXS-02 tablets found in this trial was greater than that reported for oral bisphosphonate agents

currently marketed in the United States, based on FDA package inserts. Zoledronic acid plasma concentrations after oral administration of AXS-02, measured using area under the plasma concentration curve, or AUC, and maximum plasma concentration, or C_{max}, were found to be dose proportional in the range tested using the power model.

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

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



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

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

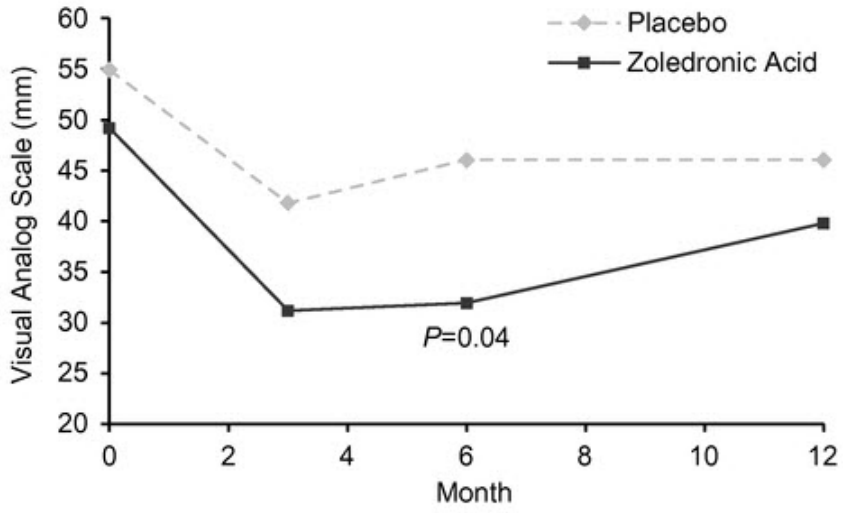
IV-administered zoledronic acid, the active molecule in AXS-02, was tested in an investigator-initiated, single-center, randomized, double-blind, placebo-controlled trial in patients with knee OA and BMLs. In this trial, zoledronic acid treatment reduced pain and BML size, as further described below,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

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

Therefore, data for this patient was included in the zoledronic acid arm in the analyses and results discussed below. This analysis is referred to as a per protocol analysis.

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

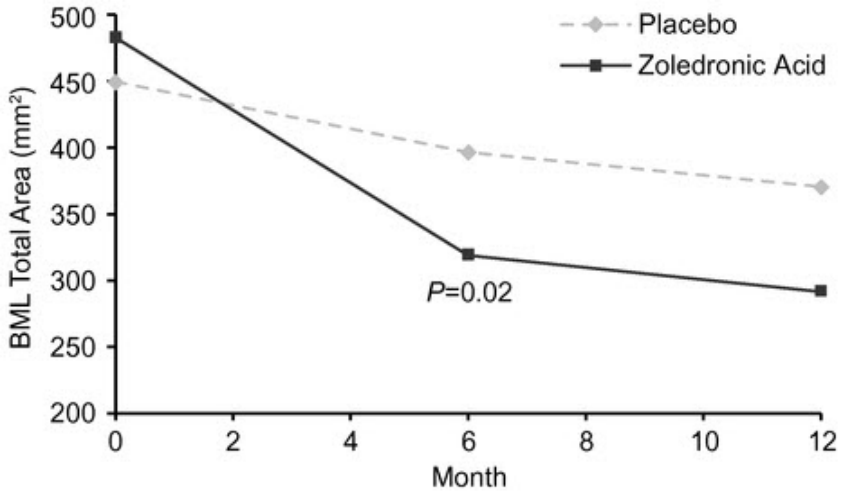
Pain intensity over time in knee OA patients with BMLs treated with zoledronic acid or placebo



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

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

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



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

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

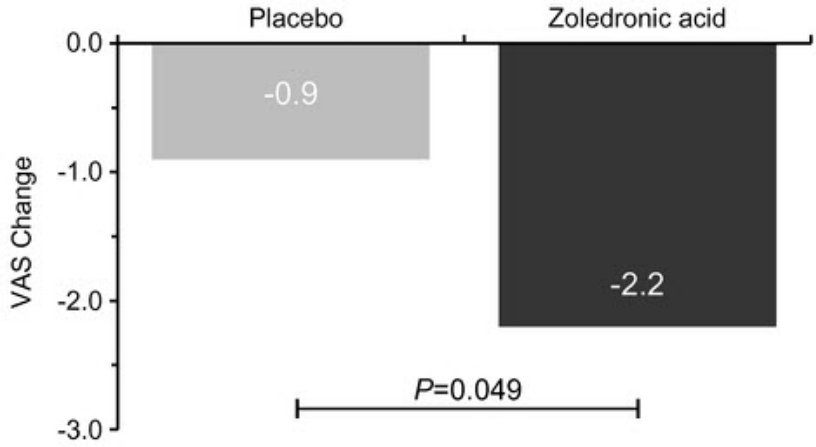
Phase 2 of Zoledronic Acid in CLBP Associated with MCs

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

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

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

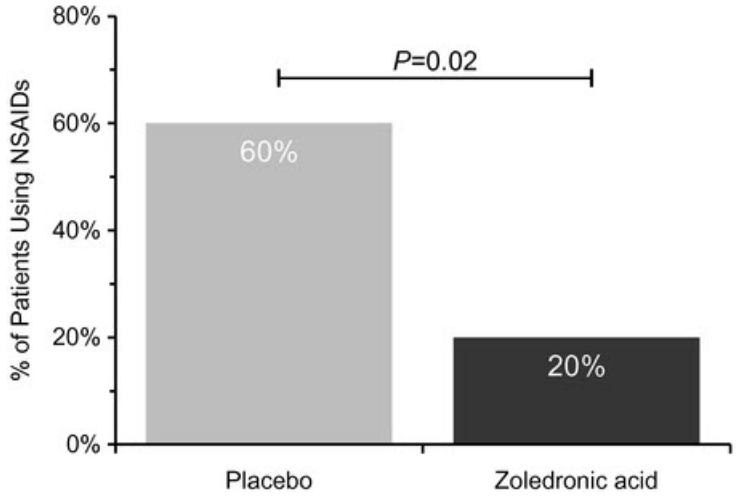
Change in pain intensity at 1 month in CLBP patients treated with zoledronic acid or placebo



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

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

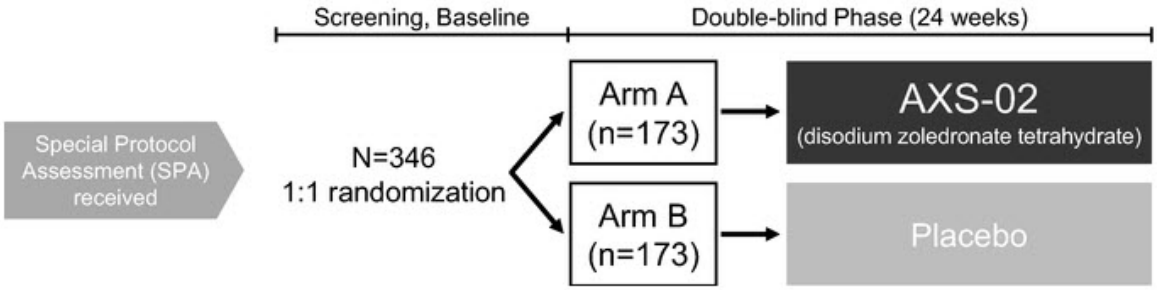
NSAID use at 1 year in CLBP patients treated with zoledronic acid or placebo



Ongoing COAST-1 Study

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

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



Planned Phase 3 Trial in CLBP Associated with MCs

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

CREATE-1 Study

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

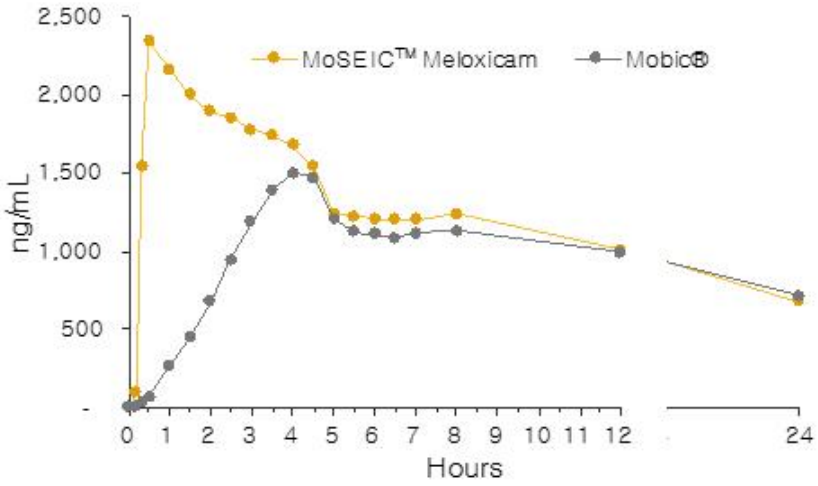
MoSEIC™ Technology

Overview

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

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

Scientific Rationale



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

AXS-07

Overview

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

Migraine

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

Indication Overview

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

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

Rationale for the Development of AXS-07 in Migraine

The rationale for combining rizatriptan with MoSEIC™ meloxicam is based on the pharmacokinetic properties of MoSEIC™ meloxicam and the efficacy of NSAIDs and triptans in migraine. By combining rizatriptan with MoSEIC™ meloxicam, AXS-07 may overcome some the limitations of triptans which include incomplete pain relief, suboptimal onset of action, and recurrence of symptoms. MoSEIC™ meloxicam contributes a distinct mechanism of action, and reaches C_{max} within 30 minutes after oral administration, thereby providing the potential for greater efficacy and a more rapid onset of action as compared to rizatriptan alone. 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 rizatriptan alone. Less recurrence would be expected to result in reduced use of rescue or repeat medication. Triptans have been shown to be efficacious for moderate to severe migraine and are considered by many the drugs of choice for the abortive treatment of attacks.

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

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

- *Strong and consistent pain relief.* AXS-07 has the potential to provide efficacy that is superior to currently available migraine treatments based on the expected additive effect of MoSEIC meloxicam and rizatriptan. Clinical experience with rizatriptan as a single agent further indicates that AXS-07 may be able to provide more consistent intra-patient efficacy than currently available migraine treatments, as well as efficacy in various stages, severities, and subtypes of migraine including menstrual migraine.

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

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

Clinical Development of AXS-07

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

We received written pre-IND meeting guidance from the FDA in August 2017 on our clinical development plan for AXS-07 in migraine. Based on that guidance, we intend to submit an IND to the FDA and we plan to conduct one Phase 3 trial of AXS-07 in the acute treatment of migraine to support an NDA filing for this indication.

AXS-06

Overview

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

Osteoarthritis and Rheumathoid Arthritis

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

Indication Overview

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

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

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

Meloxicam is a well-characterized NSAID that is approved for the treatment of the signs and symptoms of OA and RA, and is marketed under the tradename Mobic®. Meloxicam is a long-acting NSAID with COX-2 preferential inhibition. Its long half-life allows for once-daily dosing. However standard meloxicam has an extended time to maximum plasma concentration or T_{max} which may result in a slow onset of analgesic action. In addition, like other

NSAIDs, meloxicam can induce upper gastrointestinal ulcers which can be complicated by the development of bleeding, perforation or obstruction. Chronic use of NSAIDs has been reported to be associated with the development of gastrointestinal ulcers in as many as 25% of patients. AXS-06 is designed to overcome these limitations by combining a rapidly absorbed formulation of meloxicam with esomeprazole, an agent that has been proven to reduce the incidence of NSAID-associated gastrointestinal ulcers.

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

Clinical Development of AXS-06

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

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

Completed Phase 1 Trial

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

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

Commercial Agreements

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

Material License Agreements

In 2012, we entered into three exclusive license agreements with Antecip Bioventures II LLC, or Antecip, an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which we were

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

Intellectual Property

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

As of February 20, 2018, our intellectual property portfolio contains 100 issued patents and more than 80 pending applications in the United States and worldwide. 24 issued 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. 75 issued 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. One issued patent covering our AXS-07 and AXS-06 product candidates, and related compounds, has 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, Japan, 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 Axsome.

Many pharmaceutical companies, biotechnology companies, and academic institutions are competing with us in the field of pain and CNS disorders and filing patent applications potentially relevant to our business. In order to contend with the inevitable possibility of third-party intellectual property conflicts, from time to time we review and assess the third-party intellectual property landscape for competitive and other developments that may inform or impact our intellectual property development and commercialization strategies. With respect to third-party intellectual property, it is impossible to establish with certainty that our product candidates or discovery platform will be free of claims by third-party intellectual property holders or whether we will require licenses from such third parties. Even with modern databases and on-line search engines, literature searches are imperfect and may fail to identify relevant patents and published applications. Even when a third-party patent is identified, we may conclude, upon a thorough analysis, that we do not infringe the patent or that the patent is invalid. If the third-party patent owner disagrees with our conclusion and we continue with the business activity in question, we might have patent litigation forced upon us. Alternatively, we

might decide to initiate litigation in an attempt to have a court declare the third-party patent invalid or not infringed by our activity. In either scenario, patent litigation typically is costly and time consuming, and the outcome is uncertain. The outcome of patent litigation is subject to uncertainties that cannot be quantified in advance, for example, the credibility of expert witnesses who may disagree on technical interpretation of scientific data. Ultimately, in the case of an adverse outcome in litigation, we could be prevented from commercializing a product or using certain aspects of our discovery platform as a result of patent infringement claims asserted against us. This could have a material adverse effect on our business. In addition to patents, we rely upon unpatented trade secrets, know-how, and continuing technological innovation to develop and maintain a competitive position. We seek to protect our proprietary information, including our trade secrets and proprietary know-how, by requiring our employees to execute Proprietary Information, Inventions, Non-Solicitation, and Non-Competition Agreements upon the commencement of their employment. Consultants and other advisors are required to sign consulting agreements. These agreements generally provide that all confidential information developed or made known during the course of the relationship with us be kept confidential and not be disclosed to third parties except in specific circumstances. In the case of our employees, the agreements also typically provide that all inventions resulting from work performed for us, utilizing our property, or relating to our business and conceived or completed during employment shall be our exclusive property to the extent permitted by law. Further, we require confidentiality agreements from entities that receive our confidential data or materials.

Sales and Marketing

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

Scientific Advisors

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

Competition

Overview

Our industry is highly competitive and subject to rapid and significant technological change. The large size and expanding scope of the pain and CNS markets make them attractive therapeutic areas for biopharmaceutical businesses. Our potential competitors include pharmaceutical, biotechnology, and specialty pharmaceutical companies. While we

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

AXS-02 Competition

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

AXS-05 Competition

There is one product approved for the treatment of TRD, Symbyax, which is marketed by Eli Lilly and Company. In addition, Otsuka Pharmaceutical Co. Ltd. is working to develop a combination of DM and quinidine for the treatment of TRD. We are aware of several other companies developing compounds for the treatment of TRD including Alkermes plc; Allergan plc; and Janssen Research & Development, LLC. We are aware of other companies working to develop therapeutics for the treatment of agitation associated with AD, including Otsuka Pharmaceutical Co. Ltd., which is working to develop a combination of DM and quinidine in this indication; Acadia Pharmaceuticals; and Transition Therapeutics Inc. 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 gum, and lozenges.

AXS-07 Competition

There are a number of products approved for the treatment of migraine including Maxalt, which is marketed by Merck & Co., Inc. and Treximet, which is marketed by GlaxoSmithKline. We are aware of several companies developing compounds for the treatment of migraine including Alder BioPharmaceuticals, Inc., Allergan plc, Amgen Inc., and Eli Lilly and Company.

Manufacturing

Manufacturing of drugs and product candidates are done by third-parties and manufacturing of both drug substance and drug product must comply with FDA current good manufacturing practice, or cGMP, regulations. Our product candidates comprise synthetic small molecules made through a series of organic chemistry steps starting with commercially available organic chemical raw materials. We do not currently own or operate any manufacturing facilities for the clinical or commercial production of our drug candidates. We conduct manufacturing activities under individual purchase orders with independent contract manufacturing organizations, or CMOs, to supply our clinical trials. We conduct periodic quality audits of their facilities. We believe that our existing suppliers of our product candidate active

pharmaceutical ingredients and finished products will be capable of providing sufficient quantities of each to meet our clinical trial supply needs. Other CMOs may be used in the future for clinical supplies and, subject to approval, commercial manufacturing.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state, and local level, and in other countries, 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, manufacturers of pharmaceutical products participating in Medicaid and Medicare are required to comply with mandatory price reporting, discount, and rebate requirements, including anti-inflation penalties. Some states also have enacted 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.

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 to ensure the drug's identity, strength, quality, and purity;
- 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 Practices. 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. Some preclinical testing may continue even after the IND is submitted.

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

Clinical Trials

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

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

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group regularly reviews accumulated data and advises the study sponsor regarding the continuing safety of trial subjects, enrollment of potential trial subjects, and the continuing validity and scientific merit of the clinical trial. The data safety monitoring board receives special access to unblinded data during the clinical trial and may advise the sponsor to halt the clinical trial if it determined 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 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 made a condition 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 data required for the approval of an NDA, the 21st Century Cures Act provides for FDA acceptance of new kinds of data such as such as patient experience data, real world evidence for already approved products, and, for appropriate indications sought through supplemental marketing applications, data summaries.

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.

Phase 1, Phase 2, and Phase 3 clinical trials 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, manufacture, and controls, 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. These 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. Fee waivers or reductions are available in certain circumstances. One basis for a waiver of the application user fee is if the applicant employs fewer than 500 employees, including employees of affiliates, the applicant does not have an approved marketing application for a product that has been introduced or delivered for introduction into interstate commerce, and the applicant, including its affiliates, is submitting its first marketing application. 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. 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 outweigh the risks of the drug.

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

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

The FDA must refer applications for drugs that contain active ingredients, including any ester or salt of the active ingredients, that have not previously been approved by the FDA to an advisory committee or provide in an action letter a summary for not referring it to an advisory committee. The FDA may also refer drugs to advisory committees when it is determined that an advisory committee's expertise would be beneficial to the regulatory decision-making

process, including the evaluation of novel products and the use of new technology. 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.

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 the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical data or other data and information. 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 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 resubmissions in either two or six months of the resubmission date, depending on the kind of resubmission. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

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 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 upon the FDA's prior findings of safety and effectiveness for an approved product that acts as the reference listed drug or on published scientific literature, in support of its application. The FDA may also require 505(b)(2) applicants to perform additional studies or measurements to support the changes from the reference listed drug as well as bridging studies to the reference listed drug. The FDA may then approve the new product candidate for all or some of the labeled indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Orange Book Listing

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

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

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

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

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

Exclusivity

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

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

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

505(b)(2) application approval effective as a result of regulatory exclusivity or listed patents. Moreover, pediatric exclusivity attaches to all formulations, dosage forms, and indications for products with existing marketing exclusivity or patent life that contain the same active moiety as that which was studied.

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

Special FDA Expedited Review and Approval Programs

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

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

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

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

beginning as early as Phase 1 trials, and a commitment from the FDA to involve senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review.

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

Post-approval Requirements

Any product manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements related to manufacturing, recordkeeping, and reporting, including adverse experience reporting, drug shortage reporting, and periodic reporting; product sampling and distribution; advertising; marketing; promotion; certain electronic records and signatures; 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.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drug samples at the federal level. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Moreover, the Drug Quality and Security Act, or DQSA, imposes obligations on manufacturers of pharmaceutical products related to product tracking and tracing. Among the requirements of this legislation, manufacturers are required to provide certain information regarding the drug products to individuals and entities to which product ownership is transferred, will be required to label drug product with a product identifier, and are required to keep certain records regarding the drug product. The transfer of information to subsequent product owners by manufacturers is also required to be done electronically. Manufacturers are also required to verify that purchasers of the

manufacturers' products are appropriately licensed. Further, under this new legislation, manufactures have drug product investigation, quarantine, disposition, and notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products that would result in serious adverse health consequences of death to humans, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

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

Fraud and Abuse, and Transparency Laws and Regulations

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

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

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 change in Department of Justice policy now prohibits enforcement actions for knowing violations of law based on non-compliance with agency sub-regulatory guidance. 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. 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. Civil False Claims act liability may be imposed for Medicare or Medicaid overpayments, for example, overpayments caused by understated rebate amounts, that are not refunded within 60 days of discovering the overpayment, even if the overpayment was not caused by a false or fraudulent act.

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.

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

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

The VHCA also requires manufacturers of covered drugs participating in the Medicaid program to enter into Federal Supply Schedule contracts with the VA through which their covered drugs must be sold to certain federal agencies at FCP and to report pricing information. This necessitates compliance with applicable federal procurement laws and regulations and subjects us to contractual remedies as well as administrative, civil, and criminal sanctions. In

addition, the VHCA requires manufacturers participating in Medicaid to agree to provide different mandatory discounts to certain Public Health Service grantees and other safety net hospitals and clinics, and report the ceiling price to the Health Resources and Services Agency within Health and Human Services.

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

The ACA further created federal requirements for reporting, by applicable manufacturers of covered therapeutics, payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members.

Further, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its respective implementing regulations, imposes certain requirements on covered entities relating to the privacy, security, and transmission of individually identifiable health information. Among other things, HITECH, through its implementing regulations, makes HIPAA's security standards and certain privacy standards directly applicable to business associates, defined as a person or organization, other than a member of a covered entity's workforce, that performs certain functions or activities that involve the use or disclosure of protected health information on behalf of, or provides services to, a covered entity. HITECH also strengthened the civil and criminal penalties that may be imposed against covered entities, business associates, and individuals, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, other federal and state laws may govern the privacy and security of health and other information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

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

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

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

Coverage and Reimbursement Generally

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

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

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

Private payors often rely on the lead of the governmental payors in rendering coverage and reimbursement determinations. Therefore, achieving favorable CMS coverage and reimbursement is usually a significant gating issue for successful introduction of a new product. In addition, many government programs as a condition of participation

mandate fixed discounts or rebates from manufacturers regardless of formulary position or utilization, and then rely on competition in the market to attain further price reductions, which can greatly reduce realization on the sale.

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

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

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.

Healthcare Reform Measures

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

For example, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or MMA, established a new prescription drug benefit program for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Part D plans include both standalone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, which do not utilize formularies to restrict coverage, Part D coverage varies by plan. With some exceptions, Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for any products for which we

receive marketing approval. However, Part D plans use competition for coverage to leverage manufacturer rebates. Further, the law requires manufacturers to absorb a significant percentage of the prescription price paid for NDA drugs, including 504(b)(2) drugs, during a beneficiary's coverage gap. The Bipartisan Budget Act of 2018 permanently increased manufacturer liability for the prescription price in the coverage gap from 50% to 70% beginning in 2019, while simultaneously accelerating closure of the gap. These cost reduction initiatives and other provisions of the legislation, as well as any negotiated price discounts for our future products covered by a Part D prescription drug plan, may decrease the coverage and reimbursement rate that we receive, lower the net price realized on our sales to pharmacies, or both. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-governmental payors.

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

The ACA made other changes intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health care industry, and impose additional health policy reforms. The law expanded the eligibility criteria for Medicaid programs, thereby potentially increasing both the volume of sales and manufacturers' Medicaid rebate liability. The law also expanded the entities eligible for discounts under the 340B drug discount program, which mandates discounts to certain hospitals, community centers, and other qualifying providers, although, with the exception of children's hospitals, these newly eligible entities are not eligible to receive discounted 340B pricing on orphan drugs. 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 cost of pharmaceuticals continues to generate substantial governmental and third-party payor interest. Some states, such as California, have enacted transparency laws that require manufacturers to report drug price increases and related information. We expect that the pharmaceutical industry will experience pricing pressures due to the trend toward managed healthcare, the increasing influence of managed care organizations, and additional legislative proposals. 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.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. The Budget Control Act of 2011, as amended, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee on Deficit Reduction did not achieve its targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reductions to several government programs, including aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which remain in effect through 2024 unless additional Congressional action is taken. The Center for Medicare and Medicaid Services has recently promulgated rules that implement a one-third reduction of Medicare Part B reimbursement of certain hospitals for outpatient drugs purchased at a deep discount under the 340B program. 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 further limit the prices we are able to charge, or the amounts of reimbursement available, for our product candidates once they are approved.

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 $20.0 million, $21.2 million and $6.8 million for the years ended December 31, 2017, 2016, and 2015, 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-02, AXS-06, and AXS-07.

Employees

As of March 2, 2018, we had 25 full-time employees and 4 key consultants, 6 of whom hold Pharm.D., Ph.D. or M.D. degrees. None of our employees is represented by a collective bargaining agreement and we have never experienced any work stoppage. We believe that we maintain good relations with our employees.

Corporate Information

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

Available Information

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

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

ITEM 1A. RISK FACTORS.

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

RISKS RELATED TO OUR FINANCIAL CONDITION AND CAPITAL REQUIREMENTS

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

We are a clinical stage biopharmaceutical company with a limited operating history. For the last several years, we have focused our efforts primarily on developing AXS-02, AXS-05, AXS-06, AXS-07 and AXS-09, 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 $28.9 million and $27.2 million for the years ended December 31, 2017 and 2016, respectively. As of December 31, 2017, we had an accumulated deficit of $76.6 million. To date, we have not received regulatory approvals for any of our product candidates or generated any revenue from the sale of products, and we do not expect to generate any revenue in the foreseeable future. We expect to continue to incur substantial and increasing expenses and operating losses over the next several years, as we continue to develop our current and future product candidates. In addition, we expect to incur significant sales, marketing, and manufacturing expenses related to the commercialization of our current and future product candidates, if they are approved by the U.S. Food and Drug Administration, or FDA. As a result, we expect to continue to incur significant losses for the foreseeable future. We anticipate that our expenses will increase substantially as we:

- conduct our Phase 3 clinical trials with AXS-02 for the treatment of pain associated with knee osteoarthritis, or OA, associated with bone marrow lesions, or BMLs;
- conduct our Phase 3 clinical trials with AXS-05 for the treatment of treatment resistant depression, or TRD;
- conduct our Phase 3 clinical trials with AXS-05 for the treatment of agitation associated with Alzheimer's disease, or AD agitation;
- initiate and enroll patients in our Phase 3 clinical trials in other indications for AXS-02 and for AXS-05;
- continue to evaluate, plan for, and conduct, clinical trials for AXS-06 for the treatment of osteoarthritis and rheumatoid arthritis, AXS-07 for the acute treatment of migraine, and AXS-09 for the treatment of CNS disorders;
- in-license or acquire additional product candidates;
- conduct late-stage clinical trials for any product candidates that successfully complete early-stage clinical trials;
- seek regulatory approval for any product candidates that successfully complete late-stage clinical trials;
- conduct additional non-clinical studies with any product candidates;

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

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

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

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

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

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

- fund our future clinical trials for our current product candidates, especially if we encounter any unforeseen delays or difficulties in our planned development activities;

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

We believe that with our available cash as of December 31, 2017, we will have sufficient funds to meet our anticipated operating cash requirements into the third quarter of 2019. 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 November 2016, we entered into a loan and security agreement, referred to herein as the SVB Loan, with Silicon Valley Bank, or SVB, for a term loan facility in the aggregate principal amount of up to $20.0 million, of which $10.0 million was funded shortly after closing. Availability of $5.0 million under the second term advance was conditioned upon the achievement of both a clinical and financial milestone on or prior to November 9, 2017. The clinical milestone required our receipt of positive interim results of our then-ongoing CREATE-1 study of AXS-02 in CRPS, while the financial milestone required that we receive unrestricted and unencumbered net cash proceeds of at least $30.0 million from the issuance and sale of our equity securities to investors. Availability of $5.0 million under the third term advance was tied to achievement of the clinical and financial milestones described above, as well as our receipt of positive data with respect to our then-ongoing CREATE-1 study by December 31, 2017 sufficient to file a new drug application with the FDA. Because we 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.

The loan advances mature on November 1, 2020 and have an interest-only monthly payment period until December 1, 2017. Following the interest-only payment period, we will begin making monthly payments of principal and interest until the maturity date. Interest will accrue on the unpaid principal balance of the outstanding loan advances at a floating per annum rate of 4.50% above the prime rate.

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

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

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

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

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

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

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

Our product candidates will require additional clinical and non-clinical development, regulatory approval, commercial manufacturing arrangements, establishment of a commercial organization, significant marketing efforts, and further investment before we generate any revenues from product sales. We initiated our Phase 3 clinical trial with AXS-02 for the treatment of the pain of knee OA associated with BMLs in March 2016. Further, we initiated our Phase 3 clinical trial with AXS-05 for the treatment of TRD in March 2016 and for the treatment of agitation associated with AD in July 2017. 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 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, two of which were conducted with two tablets, one tablet consisting of dextromethorphan, or DM, and one tablet consisting of bupropion. Our third Phase 1 trial with AXS-05 was conducted with one tablet containing both DM and bupropion. We are also conducting our Phase 3 clinical trial with AXS-05 using one tablet containing both DM and bupropion. This change in formulation may result in a pharmacokinetic profile that is different from those observed in our completed Phase 1 trials. As a result, the FDA may request additional clinical trials, analyses, reports, data, or preclinical trials and attendant costs and delays. 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. For AXS-07, we have not conducted a Phase 1 pharmacokinetic study of one tablet consisting of MoSEIC meloxicam and rizatriptan and additional manufacturing work is required before we may submit an IND and begin late-stage clinical trials. Finally, for AXS-09, we have only completed one Phase 1 clinical trial.

Our product candidates are susceptible to the risks of failure inherent at any stage of product development, including the appearance of unexpected adverse events or failure to achieve its primary endpoints in subsequent clinical trials, including our initiated and planned Phase 3 clinical trials. For example, in January 2018, we conducted an interim analysis for our then-ongoing Phase 3 trial of AXS-02 for the treatment of CRPS, which we referred to as the CREATE-1 trial, and for our currently ongoing Phase 3 trial of AXS-02 for the treatment of the pain of knee OA associated with BMLs, which we refer to as the COAST-1 trial. Based on the recommendation we received from the independent data monitoring committee, we will continue our COAST-1 trial to full enrollment and have discontinued our CREATE-1 trial for futility. We plan to conduct two interim analyses for both the ongoing Phase 3 trial of AXS-05 in TRD and the ongoing Phase 2/3 trial of AXS-05 for the treatment of AD agitation, and 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-02 for the treatment of the pain of knee OA associated with BMLs, AXS-05 for the treatment of TRD, agitation associated with AD, and smoking cessation, and AXS-07 for the acute treatment of migraine. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. Additionally, as more fully described in "Business—Material License Agreements," we are required to pay to an entity owned by our Chief Executive Officer and Chairman of the Board certain royalty payments related to the development of AXS-02 and AXS-05, as well as AXS-04, a product candidate that is currently in early-stage development, but not with respect to the development of other product candidates, which may influence management's decision concerning which product candidates or indications to pursue. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing, or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

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

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

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

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

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

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

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

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

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

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

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

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, we would no longer be able to use the 505(b)(2) pathway. In that case, it is the FDA's policy that the appropriate submission would be an Abbreviated New Drug Application, or ANDA, for a generic version of the approved product. We may, however, not be able to immediately submit an ANDA or have an ANDA approval made effective, as we could be blocked by others' periods of patent and regulatory exclusivity protection.

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

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

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

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

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

Companies that produce branded reference listed drugs routinely bring litigation against applicants that seek regulatory approval to manufacture and market generic and reformulated forms of their branded products. These companies often allege patent infringement or other violations of intellectual property rights as the basis for filing suit. Likewise, patent holders may bring patent infringement suits against companies that are currently marketing and selling their approved generic or reformulated products. Litigation to enforce or defend intellectual property rights is often complex and often involves significant expense and can delay or prevent introduction or sale of our product candidates. If patents are held to be valid and infringed by our product candidates in a particular jurisdiction, we may be required to cease selling, relinquish or destroy existing stock, or pay monetary damages in that jurisdiction unless we can obtain a license from the patent holder. There may also be situations where we use our business judgment and decide to market and sell our approved products, notwithstanding the fact that allegations of patent infringement(s) have not been finally resolved by the courts, which is known as an "at-risk launch." The risk involved in doing so can be substantial because the remedies available to the owner of a patent for infringement may include, among other things, damages measured by the profits lost by the patent owner which may be greater than the profits earned by the infringer. In the case of willful infringement, such damages may be increased up to three times. An adverse decision in patent litigation could have a material adverse effect on our business, financial position, and results of operations and could cause the market value of our common stock to decline. Should we need to file a paragraph IV certification in the future for our product candidates, we may risk patent litigation and substantial delays.

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

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions, and may require us to amend our clinical trial protocols or conduct additional studies

that require regulatory or institutional review board, or IRB, approval, or otherwise cause delays in the approval or rejection of an application. We have not obtained regulatory approval for any product candidate and it is possible that none of our existing product candidates, or any product candidates we may seek to develop in the future, will ever obtain regulatory approval. Any delay in obtaining or failure to obtain required approvals could materially adversely affect our ability or that of any of our collaborators to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

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

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

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

- regulators or IRBs may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site or amend trial protocols;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites and our CROs;
- clinical trials of our product candidates may produce negative or inconclusive results, or our studies may fail to reach the necessary level of statistical or clinical significance, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- interim analyses may result in our clinical trials being discontinued for safety or futility reasons or may result in modifications to our clinical trials that prolong the trials or make them difficult and more expensive to complete, such as increases in the number of subjects;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, or participants may drop out of these clinical trials at a higher rate than we anticipate;

- our third-party contractors may fail to comply with regulatory requirements or the clinical trial protocol, or meet their contractual obligations to us in a timely manner, or at all, or we may be required to engage in additional clinical trial site monitoring;

- we, the regulators, or IRBs may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks, undesirable side effects, or other unexpected characteristics of the product candidate, or due to findings of undesirable effects caused by a chemically or mechanistically similar drug or drug candidate. We may also discontinue clinical research and programs due to changing business priorities;

- changes in marketing approval policies during the development period rendering our data insufficient to obtain marketing approval;

- changes in or the enactment of additional statutes or regulations;

- changes in regulatory review for each submitted product application;

- the cost of clinical trials of our product candidates may be greater than we anticipate or we may have insufficient funds for a clinical trial or to pay the substantial user fees required by the FDA upon the filing of an NDA;

- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;

- we may decide, or regulators may require us, to conduct additional clinical trials, analyses, reports, data, or preclinical trials than we currently plan, or we may abandon product development programs. For instance, with respect to our ongoing Phase 3 clinical trial with AXS-02 for the treatment of the pain of knee OA associated with BMLs, although we have received a Special Protocol Assessment, or SPA, the FDA stated that if there is a recurrence of knee OA pain, we will need to explore repeat dosing, which would require additional preclinical studies. Further, for AXS-05, we will need to conduct additional clinical and preclinical studies in addition to our Phase 3 and Phase 2/3 trials in order to file an NDA for this product candidate. Additionally, although we believe that we may be able to rely on a single pivotal study to support our NDA for AXS-07 for the acute treatment of migraine, the FDA may ultimately disagree and require us to conduct additional pivotal studies.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. Furthermore, there is the possibility that the FDA or comparable foreign regulatory authorities have not previously reviewed product candidates for the indications we are pursuing, such as bisphosphonates for the treatment of pain. As a result, we may experience delays in regulatory approval due to uncertainties in the approval process.

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

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

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

Undesirable side effects caused by our product candidates could cause us, IRBs, and other reviewing entities or regulatory authorities to interrupt, delay, or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. For example, if concerns are raised regarding the safety of a new drug as a result of undesirable side effects identified during clinical or preclinical testing, the FDA may order us to cease further development, decline to approve the drug, or issue a letter requesting additional data or information prior to making a final decision regarding whether or not to approve the drug.

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

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

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

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

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

To date, the most commonly reported adverse events observed in the completed clinical trials of AXS-05 include headache, nausea, dizziness, insomnia, dry mouth, fatigue, hypoesthesia, disturbance in attention, hyperhidrosis, increased heart rate, palpitation, constipation, diarrhea, increased blood pressure, and tremor. Some reported adverse events resulted in discontinuations from our trials of AXS-05. These adverse events included chest pain, headache, abdominal pain, diarrhea, signs of potential allergic reactions, atrial tachycardia, disturbance in attention, metamorphosia, tremor, feeling hot, dizziness, dyspnea, and increased respiratory rate. AXS-05 is a combination 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 treatement of agitation associated with AD, we exclude patients who have been treated with certain classes of medications. 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.

Our product candidates, if approved, will compete in the marketplace with other bupropion products that 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 fixed-dose 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 fixed-dose combination therapies. A fixed-dose combination therapy is a single drug product composed of two or more active ingredients, with each component making a contribution to the claimed effect of the drug. The development of fixed-dose 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 fixed-dose combinations. Finally, the FDA's requirements concerning fixed-dose combination products may change in the future.

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

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

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

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

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

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

If we are found to have impermissibly promoted any of our product candidates, we may become subject to significant liability and government fines. The FDA and other agencies actively enforce the laws and regulations regarding product promotion, particularly those prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted a product may be subject to significant sanctions. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees of permanent injunctions under which specified promotional conduct is changed or curtailed. Thus, we and any of our collaborators will not be able to promote any products we develop for indications or uses for which they are not approved.

In the United States, engaging in the impermissible promotion of our products, following approval, for off-label uses can also subject us to false claims and other litigation under federal and state statutes, including fraud and abuse and consumer protection laws, which can lead to civil and criminal penalties and fines, agreements with governmental authorities that materially restrict the manner in which we promote or distribute drug products and do business through, for example, corporate integrity agreements, suspension or exclusion from participation in federal and state healthcare

programs, and debarment from government contracts and refusal of future orders under existing contracts. These false claims statutes include the federal civil False Claims Act, which 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 activities violate its regulations and policies pertaining to product promotion, it could request that we modify our promotional materials 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, untitled, or cyber 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 harmonised 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 a new regulation coming into force on 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: Alder Biopharmaceuticals, Inc.; Alkermes plc; Allergan plc; Amgen Inc.; Carbylan Therapeutics, Inc.; Eli Lilly and Company; Flexion Therapeutics, Inc.; Grunenthal GmbH; Janssen Research & Development, LLC; Levolta Pharmaceuticals, Inc.; Otsuka Pharmaceutical Co. Ltd.; OPKO Health, Inc.; Acadia Pharmaceuticals, Inc.; and Intra-Cellular Therapies, 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.

We are not aware of any generic products currently available on the market that are approved for the specific indications that we are pursuing; however, generic forms of the active ingredients of our product candidates, including zoledronic acid, DM, and bupropion, are available and could be used off-label. Any such off-label use could adversely affect our profitability and have a negative effect on our operating results and financial condition. For example, even though zoledronic acid is not currently approved for the treatment of pain, we would not be able to prevent a physician from prescribing zoledronic acid in intravenous form for such treatment. Nor could we prevent a payor from offering favorable coverage for such product and disadvantaging our product candidates, even if the generics would be used off-label.

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

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

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

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

Further, if we do not file a patent infringement lawsuit against a generic manufacturer within 45 days of receiving notice of its paragraph IV certification, the ANDA or 505(b)(2) applicant would not be subject to a 30-month

stay. Litigation or other proceedings to enforce or defend intellectual property rights are often very complex in nature, may be expensive and time consuming, may divert our management's attention from our core business, and may result in unfavorable results that could adversely impact our ability to prevent third parties from competing with our products. Accordingly, upon approval of our product candidates we may be subject to generic competition or competition from similar products, or may need to commence patent infringement proceedings, which would divert our resources.

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

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

AXS-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-02 received Orphan Drug Designation from the FDA for the treatment of CRPS. Although we are no longer pursuing 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 European Union for this indication for a period of at least 10 to 12 years.

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

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

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

We have no prior experience in the marketing, sale, and distribution of pharmaceutical products, and there are significant risks involved in the building and managing of a commercial infrastructure. The establishment and development of our own sales force and related compliance plans to market any products we may develop will be expensive and time consuming and could delay any product launch, and we may not be able to successfully develop this capability. We, or our future collaborators, will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train, manage, and retain marketing and sales personnel. In the event we are unable to develop a marketing and sales infrastructure, we may not be able to commercialize any of our current or future product candidates, which would limit our ability to generate product revenues. Factors that may inhibit our efforts to commercialize any of our current or future product candidates on our own include:

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

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

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

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

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

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

- the efficacy of our product candidates;
- the prevalence and severity of adverse events associated with such product candidate;
- the clinical indications for which the product is approved and the approved claims that we may make for the product;
- limitations or warnings contained in the product's FDA-approved labeling, including potential limitations or warnings for such product candidate, that may be more restrictive than other competitive products;
- changes in the standard of care for the targeted indications for such product candidate, which could reduce the marketing impact of any claims that we could make following FDA approval, if obtained;
- the relative convenience and ease of administration of such product candidate;
- cost of treatment versus economic and clinical benefit in relation to alternative treatments or therapies;

- the availability of adequate coverage or reimbursement by third parties, such as insurance companies and other healthcare payors, and by government healthcare programs, including Medicare and Medicaid;
- the willingness of third party payors to prefer similar but less expensive products even if not approved for our product's indication;
- the extent and strength of our marketing and distribution of such product candidate;
- the safety, efficacy, and other potential advantages over, and availability of, alternative treatments already used or that may later be approved for any of our intended indications;
- distribution and use restrictions imposed by the FDA with respect to such product candidate or to which we agree as part of a mandatory risk evaluation and mitigation strategy or voluntary risk management plan;
- the timing of market introduction of such product candidate, as well as competitive products;
- our ability to offer such product candidate for sale at competitive prices, including prices that are competitive with generic products;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the clinical indications for which such product candidate is approved;
- the extent and strength of our third-party manufacturer and supplier support;
- the approval of other new products for the same indications;
- adverse publicity about the product or favorable publicity about competitive products; and
- potential product liability claims.

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

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

The potential market opportunities for our product candidates are difficult to precisely estimate. Our estimates of the potential market opportunities are predicated on many assumptions including industry knowledge and

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

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

The use of any of our current or future product candidates in clinical trials, and the sale of any of our product candidates for which we obtain regulatory approval, exposes us to the risk of product liability claims. We face inherent risk of product liability related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any product candidates that we may develop. For example, we may be sued if any product candidate we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing, or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. Product liability claims might be brought against us by consumers, healthcare providers, or others using, administering, or selling our products. If we cannot successfully defend ourselves against these claims, we will incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of merit or eventual outcome, liability claims may result in:

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

We have obtained limited product liability insurance coverage for our products and our clinical trials with a $8 million annual aggregate coverage limit. We have also obtained local policies in those foreign jurisdictions where it was appropriate. However, our insurance coverage may not reimburse us or may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against

losses due to liability. We intend to expand our insurance coverage to include the sale of commercial products if we obtain FDA approval for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing, or at all. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business and our prospects.

RISKS RELATED TO OUR DEPENDENCE ON THIRD PARTIES

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

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

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

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

We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product candidates that were produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register

certain clinical trials and post the results of certain completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in enforcement actions and adverse publicity.

Our CROs may also have relationships with other entities, some of which may be our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, non-clinical, and preclinical programs. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed, or terminated and we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates, or we or they may be subject to regulatory enforcement actions. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. To the extent we are unable to successfully identify and manage the performance of third-party service providers in the future, our business may be materially and adversely affected.

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

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

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

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

Any problems or delays we experience in preparing for commercial-scale manufacturing of a product candidate may result in a delay in FDA approval of the product candidate or may impair our ability to manufacture commercial quantities or such quantities at an acceptable cost, which could result in the delay, prevention, or impairment of clinical development and commercialization of our product candidates and could adversely affect our business. For example, our manufacturers will need to produce specific batches of our product candidates to demonstrate acceptable stability under various conditions and for commercially viable lengths of time. We and our contract manufacturers will need to demonstrate to the FDA and other regulatory authorities that this is acceptable stability data for our product candidates, as well as validate methods and manufacturing processes, in order to receive regulatory approval to commercialize any of our current or future product candidates. Furthermore, if our commercial manufacturers fail to deliver the required commercial quantities of bulk drug substance or finished product on a timely basis and at commercially reasonable prices, we would likely be unable to meet demand for our products and we would lose potential revenues.

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

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

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

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

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

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

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

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

Our business model is to commercialize our product candidates in the United States and generally to seek future collaboration arrangements with pharmaceutical or biotechnology companies for the development or commercialization of our product candidates in the rest of the world. We currently have not entered into any sub-license agreements. Our 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. 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 for the development and potential commercialization of any of our current or future product candidates. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for collaboration will depend upon, among other things, our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms, or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform and our business may be materially and adversely affected.

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

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

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

In 2012, we entered into three exclusive license agreements with Antecip Bioventures II LLC, or Antecip, an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which we were granted exclusive licenses to develop, manufacture, and commercialize Antecip's patents and applications related to the development of AXS-02 and AXS-05, as well as AXS-04, a product candidate that is currently in early stage development, anywhere in the world for veterinary and human therapeutic and diagnostic use. The agreements were amended in August 2015 to update the schedule of patents and applications subject to the license agreements. Pursuant to the agreements, we are required to use commercially reasonable efforts to develop, obtain regulatory approval for, and commercialize AXS-02, AXS-05, and AXS-04. Under the terms of the agreements, we are required to pay to Antecip a

royalty equal to 4.5% for AXS-02, 3.0% for AXS-05, and 1.5% for AXS-04, of net sales of products containing the licensed technology by us, our affiliates, or permitted sublicensees. These royalty payments are subject to reduction by an amount up to 50.0% of any required payments to third parties. Unless earlier terminated by a party for cause or by us for convenience, the agreements remain in effect on a product-by-product and country-by-country basis until the later to occur of (1) the applicable product is no longer covered by a valid claim in that country or (2) 10 years from the first commercial sale of the applicable product in that country. Upon expiration of the agreements with respect to a product in a country, our license grant for that product in that country will become a fully paid-up, royalty-free, perpetual non-exclusive license. If Antecip terminates any of the agreements for cause, or if we exercise our right to terminate any of the agreements for convenience, the rights granted to us under such terminated agreement will revert to Antecip. To date, we have not been required to make any payments to Antecip under any of the license agreements. If any of the license agreements with Antecip are terminated for any reason, our business, financial condition, results of operations, and prospects will be materially harmed.

RISKS RELATED TO INTELLECTUAL PROPERTY

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

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

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

- we may not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
- we may not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our product candidates or technologies;
- it is possible that none of the pending patent applications will result in issued patents;

- the issued patents may not cover commercially viable active products, may not provide us with any competitive advantages, or may be successfully challenged by third parties;
- we may not develop additional proprietary technologies that are patentable;
- patents of others may have an adverse effect on our business;
- noncompliance with governmental patent agencies requirements can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction, potentially allowing competitors to enter the market earlier than would otherwise have been the case;
- our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with, or eliminate our ability to make, use, and sell our potential product candidates; or
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of available patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns.

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

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

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

The USPTO has developed regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, did not become effective until March 16, 2013. However, the full impact of the Leahy-Smith Act and the

courts' review of any appeals to related proceedings, is in its early stages. Accordingly, the full impact that the Leahy-Smith Act will have on the operation of our business is not clear. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, as well as our ability to bring about timely favorable resolution of any disputes involving our patents and the patents of others. Patent applications in the United States are maintained in confidence for at least 18 months after their earliest effective filing date. Consequently, we cannot be certain we were the first to invent or the first to file patent applications on AXS-02, AXS-05, or any other of 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 and October 2017, petitions for post-grant review of U.S. Patent No. 9,408,862, which we refer to as the '862 patent, and of U.S. Patent No. 9,539,268, which we refer to as the '268 patent, respectively, 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 petitions request that the Patent Trial and Appeal Board, or PTAB, initiate proceedings to review the validity of the '239, the '862, and the '268 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. We cannot predict what the outcomes of the proceedings for the '239 patent will be. 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. Any patent claim the PTAB determines to be unpatentable as a result of these proceedings would be stricken from the challenged patents or modified. We cannot predict if the PTAB will initiate a proceeding on the '862 patent, or what the outcomes of the proceeding would be if it is initiated. If the PTAB decides to

initiate a proceeding, it may determine that all the claims of the challenged patent are unpatentable. In February 2018, we responded to and opposed the petition for the '268 patent. The PTAB is expected to render a decision as to whether it will initiate a post-grant review for that patent. Any patent claim the PTAB determines to be unpatentable as a result of these proceedings would be stricken from the challenged patents or modified. We cannot predict if the PTAB will initiate a proceeding on the '268 patent, or what the outcomes of the proceeding would be if it is initiated. If the PTAB decides to initiate a proceeding, it may determine that all the claims of the challenged patent are unpatentable. Additionally, we cannot be sure that the validity of the claims in other issued patents covering any of our current or future product candidates will not also be challenged, or that Grunenthal will not file any additional petitions for post-grant review with respect to any of our current or future product candidates. We may incur increased expenses related to the growth of our intellectual property portfolio and to its defense.

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

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

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

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

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

Our ability to develop, manufacture, market, and sell any of our current and future product candidates depends upon our ability to avoid infringing the proprietary rights of third parties, and our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market, and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual

property litigation in the biotechnology and pharmaceutical industries. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the general field of treatment and management of pain and other CNS disorders and cover the use of numerous compounds and formulations in our targeted markets. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. Because of the uncertainty inherent in any patent or other litigation involving proprietary rights, we and our licensors may not be successful in defending intellectual property claims by third parties, which could have a material adverse effect on our business, financial condition, results of operations, and prospects. Regardless of the outcome of any litigation, defending the litigation may be expensive, time consuming, and distracting to management. In addition, because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that any of our current or future product candidates may infringe. There could also be existing patents of which we are not aware that any of our current or future product candidates may inadvertently infringe.

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

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

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

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

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

other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

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

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

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

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

As is common in the biotechnology and pharmaceutical industry, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these individuals or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

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

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

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

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

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our or our licensors' intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

RISKS RELATED TO LEGAL AND COMPLIANCE MATTERS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In January 2017, the U.S. House of Representatives and Senate passed legislation, which, if signed into law by the current administration, would repeal certain aspects of the ACA. Further, on January 20, 2017, the current administration signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Further, in December 2017, the current administration signed into law legislation that repealed the individual mandate in the ACA and increased manufacturer liability for payment on behalf of Medicare Part D beneficiaries during the coverage gap. Congress also could consider additional legislation to repeal and replace elements of the ACA.

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

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

In addition, there have been a number of other legislative and regulatory proposals aimed at changing the pharmaceutical industry. For instance, the enacted Drug Quality and Security Act imposes obligations on manufacturers of pharmaceutical products related to product tracking and tracing. Among the requirements of this legislation, manufacturers are required to provide certain information regarding the drug product to individuals and entities to which product ownership is transferred, will be required label drug product with a product identifier, and are required to keep certain records regarding the drug product. The transfer of information to subsequent product owners by manufacturers is also required to be done electronically. Manufacturers are also required to verify that purchasers of the manufacturers' products are appropriately licensed. Further, under this legislation, manufactures have drug product investigation,

quarantine, disposition, and FDA and trading partner notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products that would result in serious adverse health consequences of death to humans, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

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 European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. There can be no assurance that our products will be considered cost-effective by third-party payors, that an adequate level of reimbursement will be available, or that the third-party payors' reimbursement policies will not adversely affect our ability to sell our products profitably. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

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

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees, independent contractors, consultants, commercial partners, principal investigators, or CROs could include intentional, reckless, negligent, or unintentional failures to comply with FDA regulations, comply with applicable fraud and abuse laws, provide accurate information to the FDA, report financial information or data accurately, or disclose unauthorized activities to us. This misconduct could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter this type of misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, and results of operations, including the imposition of significant fines or other sanctions.

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

Manufacturing activities for the production of our product candidates involve the controlled storage, use, and disposal of hazardous materials, including the components of our product candidates, and other hazardous compounds. Our third-party manufacturers and we are subject to federal, state, and local laws and regulations governing the use, manufacture, storage, handling, release, and disposal of, and exposure to, these hazardous materials. Violation of these laws and regulations could lead to substantial fines and penalties. Although we believe that our safety procedures, and those of our third-party manufacturers, for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these

materials. In the event of an accident, state or federal authorities may curtail our use of these materials and interrupt our business operations. In addition, we could become subject to potentially material liabilities relating to the investigation and cleanup of any contamination, whether currently unknown or caused by future releases.

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

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

RISKS RELATED TO OUR BUSINESS OPERATIONS

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

As of March 2, 2018, we had only 25 full-time employees and 4 key consultants. We will need to substantially expand our managerial, commercial, financial, manufacturing, and other personnel resources in order to manage our operations and prepare for the commercialization of our product candidates, if approved. Our management, personnel, systems, and facilities currently in place may not be adequate to support this future growth. In addition, we may not be able to recruit and retain qualified personnel in the future, particularly for sales and marketing positions, due to competition for personnel among pharmaceutical businesses, and the failure to do so could have a significant negative impact on our future product revenues and business results. Our need to effectively manage our operations, growth and various projects requires that we:

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

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

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

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

delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure you that, following any such acquisition, we will achieve the expected synergies to justify the transaction.

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

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

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

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

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

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

Our testing, or the subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses. We will incur substantial accounting expense and expend significant management efforts to comply with internal control over financial reporting requirements. We currently do not have an internal audit group, and we may need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge. Moreover, if we are not able to comply with these requirements in a timely manner or if we or our independent registered public accounting

firm identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline, and we could be subject to sanctions or investigations by the Nasdaq Global Market, the SEC or other regulatory authorities, which would require additional financial and management resources.

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

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

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

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

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

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

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

of personal, confidential, or proprietary information, we could incur liability and the further development of any of our product candidates could be delayed.

RISKS RELATED TO OWNERSHIP OF OUR COMMON STOCK

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

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

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

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

- delays in the commencement, enrollment, and ultimate completion, of our planned and ongoing Phase 3 clinical trials for our product candidates;
- any delay or refusal on the part of the FDA in approving an NDA for any of our current and future product candidates;
- the commercial success of any of our current and future product candidates, if approved by the FDA;
- results of clinical trials of any of our current and future product candidates or those of our competitors;
- actual or anticipated variations in quarterly or annual operating results;
- failure to meet or exceed financial projections we provide to the public, if any;
- failure to meet or exceed the estimates and projections of the investment community, including securities analysts;
- introduction of competitive products or technologies;
- changes or developments in laws or regulations applicable to our product candidates;
- the perception of the pharmaceutical industry by the public, legislatures, regulators, and the investment community;
- general economic and market conditions and overall fluctuations in U.S. equity markets;
- data or security breaches;
- developments concerning our sources of manufacturing supply, warehousing, and inventory control;

- disputes or other developments relating to patents or other proprietary rights;
- additions or departures of key scientific or management personnel;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- capital commitments;
- investors' general perception of our company and our business;
- announcements and expectations of additional financing efforts, including the issuance of debt, equity or convertible securities;
- sales of our common stock, including sales by our directors and officers or significant stockholders;
- changes in the market valuations of companies similar to us;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, or divestitures;
- general conditions or trends in our industry; and
- the other factors described in this "Risk Factors" section.

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

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

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

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

Our quarterly operating results may fluctuate significantly.

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

- whether the FDA requires us to complete additional, unanticipated studies, tests, or other activities prior to approving any of our current and future product candidates, which would likely further delay any such approval;

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

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

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, grants, and license and development agreements in connection with any collaborations. We do not have any committed external source of funds. To the extent that we raise additional capital by issuing equity securities, our existing stockholders' ownership will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, or declaring dividends.

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

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

As of March 2, 2018, our executive officers, directors, and 5% stockholders and their affiliates beneficially owned an aggregate of approximately 43.4% of our outstanding common stock. As a result, these stockholders have significant influence and may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This concentration of ownership could delay or prevent any acquisition of our company on terms that other stockholders may desire, and may adversely affect the market price of our common stock.

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

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

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

As of March 2, 2018, we have outstanding 25,492,992 shares of common stock and 4,414,787 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, 17,442,851 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 5,257,843 shares of common stock subject to options or other equity awards issued or reserved for future issuance under our 2015 Omnibus Incentive Compensation 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 March 2017 public offering, our December 2017 registered direct offering, and any proceeds from sales pursuant to the 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, including our March 2017 public offering, our December 2017 registered direct offering and proceeds from sales pursuant to our “at-the-market” sales agreement with Leerink Partners LLC, or the Sales Agreement, if any, and our stockholders will not have the opportunity as part of their investment decision to assess whether the net proceeds from those capital raises are being used appropriately. You may not agree with our decisions, and our use of the proceeds may not yield any return on your investment. Because of the number and variability of factors that will determine our use of

the net proceeds from our capital raises, including our March 2017 public offering, our December 2017 registered direct offering and proceeds from sales pursuant to the Sales Agreement, if any, their ultimate use may vary substantially from their currently intended use. Our failure to apply the net proceeds of our capital raises, including our March 2017 public offering, our December 2017 registered direct offering and proceeds from sales pursuant to the Sales Agreement, if any, effectively could compromise our ability to pursue our growth strategy and we might not be able to yield a significant return, if any, on our investment of those net proceeds. You will not have the opportunity to influence our decisions on how to use our net proceeds from those capital raises, including our March 2017 public offering, our December 2017 registered direct offering and proceeds from sales pursuant to the Sales Agreement, if any. Pending their use, we may invest the net proceeds from our capital raises, including our March 2017 public offering and December 2017 registered direct offering, in short-term, investment-grade, interest-bearing instruments and U.S. government securities. These temporary investments are not likely to yield a significant return.

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

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

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

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

Our net operating loss carryforwards and any future research and development tax credits may expire and not be used. As of December 31, 2017, we had U.S. net operating loss carryforwards of approximately $61 million. Our net operating loss carryforwards arising in taxable years ending on or prior to December 31, 2017 will begin expiring in 2033 if we have not used them prior to that time. 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 and December 2017 registered direct offering, private placements and other transactions that have occurred, may trigger, or may have already triggered, such an ownership change. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo further ownership changes in the future. We have never completed an analysis as to whether such a change of ownership has occurred, but in such an event, we will be limited regarding the amount of net operating loss carryforwards and research tax credits that could be utilized annually in the future to offset taxable income or tax, respectively. Any such annual limitation may significantly reduce the utilization of the net operating loss carryforwards and research tax credits before they expire. In addition, certain states have suspended use of net operating loss carryforwards for certain taxable years, and other states

are considering similar measures. As a result, we may incur higher state income tax expense in the future. Depending on our future tax position, continued suspension of our ability to use net operating loss carryforwards in states in which we are subject to income tax could have an adverse impact on our results of operations and financial condition.

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

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

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

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

In addition, we are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, 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 Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws, or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage such lawsuits against us and our directors, officers, and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 2. PROPERTIES.

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

ITEM 3. LEGAL PROCEEDINGS.

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

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

Part II

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

Market Information

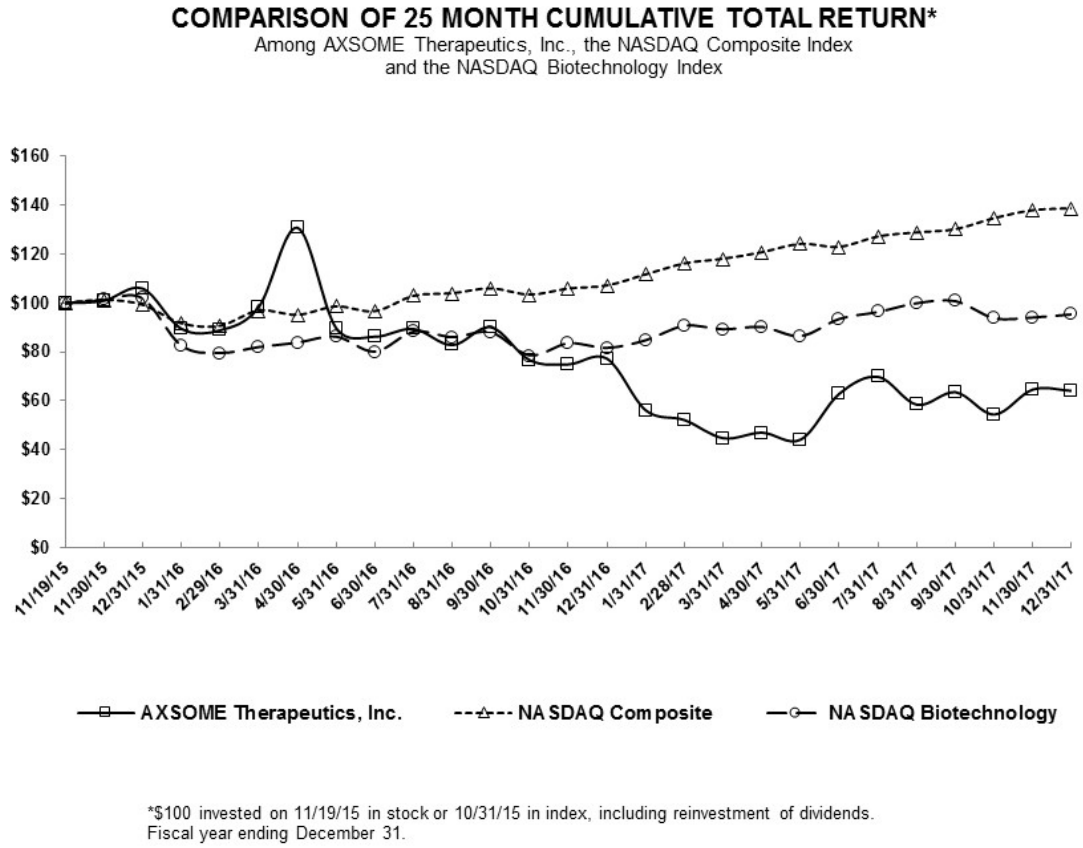
Our common stock has been listed on the Nasdaq Global Market since March 3, 2017 under the symbol "AXSM". Prior to that, our common stock was listed on the Nasdaq Capital Market since November 19, 2015, under the symbol "AXSM.". Prior to our initial public offering, there was no public market for our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

The following table sets forth the high and low sale prices of our common stock for the periods indicated.

	High	Low
Year Ended December 31, 2017		
Fourth Quarter	$ 6.45	$ 4.40
Third Quarter	$ 6.40	$ 4.45
Second Quarter	$ 6.09	$ 3.53
First Quarter	$ 7.10	$ 3.55
Year Ended December 31, 2016		
Fourth Quarter	$ 9.11	$ 5.25
Third Quarter	$ 8.35	$ 6.85
Second Quarter	$ 12.69	$ 6.06
First Quarter	$ 15.74	$ 5.37

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, 2017 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.



Holders

The number of record holders of our common stock as of March 2, 2018 was 30. 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, preclude us from paying cash dividends without SVB's consent.

Use of Proceeds from Initial Public Offering of Common Stock

On November 19, 2015, our Registration Statement on Form S-1, as amended (File No. 333-207393) was declared effective in connection with the initial public offering of our common stock, pursuant to which we sold 5,666,667 shares at a public offering price of $9.00 per share. The initial public offering closed on November 24, 2015, as a result of which we received gross proceeds of approximately $51.0 million and net proceeds of approximately $45.5 million, after deducting underwriting discounts and commissions of approximately $3.6 million and offering-related transaction costs of approximately $1.9 million.

As of December 31, 2017, we have spent $45.5 million of our net proceeds from the IPO primarily to fund the Phase 3 clinical trials for AXS-02 and AXS-05, as well as general working capital purposes, which represents all of the funds raised in our IPO.

There has been no material change in the planned use of proceeds from our initial public offering as described in our final prospectus filed with the SEC pursuant to Rule 424(b) under the Securities Act on November 19, 2015.

ITEM 6. SELECTED FINANCIAL DATA.

The following Statement of Operations Data for the years ended December 31, 2017, 2016 and 2015 and Balance Sheet Data as of December 31, 2017, 2016 and 2015, 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,		
	2017	2016	2015
Statements of operations data:			
Operating expenses:			
Research and development	$ 19,957,616	$ 21,199,860	$ 6,776,987
General and administrative	7,206,691	6,343,648	2,419,289
Total operating expenses	27,164,307	27,543,508	9,196,276
Loss from operations	(27,164,307)	(27,543,508)	(9,196,276)
Interest and amortization of debt discount expense	(1,340,199)	(132,424)	(736,048)
Tax credit	207,114	474,279	—
Change in fair value of warrant liability	(646,000)	—	(108,539)
Change in fair value of embedded derivative liabilities	—	—	274,800
Loss on extinguishment of debt	—	—	(2,444,516)
Net loss	$ (28,943,392)	$ (27,201,653)	$ (12,210,579)
Weighted average common shares outstanding—basic and diluted	22,764,606	19,150,690	11,945,318
Net loss per common share—basic and diluted	$ (1.27)	$ (1.42)	$ (1.02)

	As of December 31,		
	2017	2016	2015
Balance sheet data:			
Cash	$ 34,021,123	$ 36,618,497	$ 48,036,260
Total assets	35,555,564	38,212,608	49,076,156
Total current liabilities	12,175,336	7,170,712	2,631,895
Loan payable, long-term, net of discounts	6,663,005	9,470,445	—
Accumulated deficit	(76,584,843)	(47,641,451)	(20,439,798)
Total stockholders' equity	$ 16,717,223	$ 21,571,451	$ 46,444,261

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 product candidate portfolio includes five CNS product candidates, AXS-05, AXS-09, AXS-02, AXS-07, and AXS-06 which we are developing for multiple indications. We are conducting a Phase 3 trial with AXS-05 in treatment resistant depression, or TRD, which we refer to as the STRIDE-1 study, and a Phase 2/3 trial in agitation associated with Alzheimer's disease, or AD, which we refer to as the ADVANCE-1 study. Additionally, AXS-05 is being developed for smoking cessation. AXS-09 is being developed for CNS disorders. We are also conducting a Phase 3 trial with AXS-02 in knee osteoarthritis, or OA, associated with bone marrow lesions, or BMLs, pursuant to a Special Protocol Assessment, or SPA, which we refer to as the COAST-1 study. We also plan to initiate a Phase 3 trial with AXS-02 in chronic low back pain, or CLBP, associated with Modic changes, or MCs. AXS-07 is initially being developed for the acute treatment of migraine. Lastly, AXS-06 is being developed for the treatment of osteoarthritis and rheumatoid arthritis and for the reduction of the risk of nonsteroidal anti-inflammatory drug, or NSAID, associated gastric ulcers. Additionally, we are currently evaluating other preclinical product candidates, which we intend to develop for CNS disorders. We aim to become a fully integrated biopharmaceutical company that develops and commercializes differentiated therapies that expand the treatment options available to caregivers and improve the lives of patients living with CNS disorders.

AXS-05, is an innovative oral fixed-dose combination of dextromethorphan, or DM, and bupropion. We are developing AXS-05 initially for the following three indications: TRD, agitation associated with AD, and as an aid to smoking cessation. DM is active at multiple CNS receptors but is rapidly and extensively metabolized in humans. As a result, it is difficult to attain potential therapeutic plasma levels of DM when it is dosed as a single agent. AXS-05 uses bupropion as a novel drug delivery method to inhibit DM metabolism and increase its bioavailability. We have demonstrated in three Phase 1 trials that DM plasma levels are substantially increased into a potentially therapeutic range with the co-administration of bupropion. Bupropion is itself active at distinct CNS receptors providing the potential for an additive or synergistic effect. We intend to seek FDA approval for AXS-05 utilizing the 505(b)(2) regulatory development pathway.

AXS-09 is a novel, oral medicine combination 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-02, disodium zoledronate tetrahydrate, is a potentially first-in-class, oral, targeted, non-opioid therapeutic for chronic pain. AXS-02 is a potent inhibitor of osteoclasts, which are bone remodeling cells that break down bone tissue. We are initially developing AXS-02 for the treatment of pain in the following two conditions: knee OA associated

with BMLs and CLBP associated with type 1 or mixed type 1 and type 2 MCs. These conditions exhibit target lesions or specific pathology that we believe may be addressed by the mechanisms of action of AXS-02, such as inhibition of osteoclast activity. These mechanisms may result in a reduction of pain in these conditions. We have successfully completed a Phase 1 trial of AXS-02 to characterize the pharmacokinetics of zoledronic acid and its effects on markers of bone resorption after oral administration of AXS-02. The results of our Phase 1 trial demonstrated that oral administration of AXS-02 tablets resulted in rapid absorption of zoledronic acid, which is the active molecule in AXS-02 and the free acid form of disodium zoledronate tetrahydrate, and substantial suppression of bone resorption markers, which are proteins indicative of bone tissue breakdown. We intend to seek FDA approval for AXS-02 utilizing the 505(b)(2) regulatory development pathway.

AXS-07, is a novel, oral, fixed-dose combination 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-HT1B/D agonist that inhibits calcitonin gene-related peptide (CGRP)-mediated vasodilation, has been shown to have central trigeminal antinociceptive activity, and may reduce the release of inflammatory mediators from trigeminal nerves. Rizatriptan is approved as a single agent for the acute treatment of migraine. We intend to seek FDA approval for AXS-07 utilizing the 505(b)(2) regulatory development pathway.

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

Since our incorporation in January 2012, our operations to date have included organizing and staffing our company, business planning, raising capital, developing our compounds, and engaging in other discovery and preclinical activities. Prior to our initial public offering, or IPO, in November 2015, we financed our operations primarily through private placements of our convertible notes.

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 Silicon Valley Bank, or SVB, for a term loan of up to $20.0 million. The initial tranche of $10.0 million was funded shortly after executing the loan agreement. As discussed in greater detail elsewhere in this Annual Report on Form 10-K, because we did not achieve the conditional criteria to access the second and third tranches before the specified dates, the additional $10.0 million in additional term loan advances expired.

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 a sales agreement, or the “Sales Agreement”, with Leerink Partners LLC or "Leerink", pursuant to which we may sell up to $30 million in shares of our common stock from time to time through Leerink, acting as its sales agent, in one or more at-the-market offerings. Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the Sales Agreement. Gross sales of $0.1 million were made under the Sales Agreement during the year ended December 31, 2017.

In December 2017, we completed a registered direct offering priced at the market, whereby we sold 1,783,587 shares of our common stock and warrants to purchase up to an aggregate of 1,783,587 shares of its common stock at a combined purchase price of $5.325 per share. Additionally, we issued warrants to the placement agent to purchase 107,015 shares of our common stock at an exercise price of $6.6562 per share. We received gross proceeds of approximately $9.5 million and net proceeds of approximately $8.8 million, net of underwriting discounts and offering expenses.

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 $28.9 million, $27.2 million, and $12.2 million for the years ended December 31, 2017, 2016, and 2015, respectively. Our accumulated deficit as of December 31, 2017 was $76.6 million, and we expect to incur significant expenses and increasing operating losses for the foreseeable future. We expect our expenses to increase in connection with our ongoing activities, as we continue the development and clinical trials of, and seek regulatory approval for, AXS-02, AXS-05, AXS-06, AXS-07, AXS-09, 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 or debt financings or other sources. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy. We will need to generate significant revenue to achieve profitability, and we may never do so.

Financial Overview

Revenue

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

Research and Development Expenses

Research and development expenses primarily 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, 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, 2017, 2016 and 2015:

	Year ended December 31,		
	2017	2016	2015
AXS-02	$ 6,775,736	$ 9,414,980	$ 3,737,421
AXS-05	9,780,593	8,444,618	678,273
AXS-06	480,425	353,957	182,744
AXS-07	180,255	—	—
Other research and development	2,126,978	1,870,679	1,555,648
Stock-based compensation	613,629	1,115,626	622,901
Total research and development expenses	$ 19,957,616	$ 21,199,860	$ 6,776,987

Other research and development expenses primarily consist of employee salaries and benefits, facilities and overhead costs, and expenses for terminated programs.

General and Administrative Expenses

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

Interest and Amortization of Debt Discount Expense

Interest and amortization of debt discount expense primarily consists of cash interest and non-cash costs related to our term loan with SVB, which was entered into in 2016, as well as cash and non-cash interest costs related to the

convertible debt we had outstanding in 2015. We record costs incurred in connection with the issuance of debt as a direct deduction from the debt liability. 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 the amortization of the premium recognized due to extinguishment of debt, as well as interest income earned on cash.

Tax Credit

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

Change in Fair Value of Warrant Liability

The warrants to purchase our common stock issued as part of the registered direct stock offering in December 2017 and warrants to purchase our common stock issued to the placement agent in connection with our convertible notes issued in 2014 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.

Change in Fair Value of Embedded Derivative Liabilities

We issued convertible notes from September 2014 through July 2015 that included an embedded derivative that required bifurcation from the host debt instrument. We aggregated these bifurcated features and reflected the values of these embedded derivatives in the account “embedded derivative liabilities” which 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 embedded derivative liabilities.

Loss on Extinguishment of Debt

During June 2014, we amended our convertible notes issued from June 2013 through October 2013 in order to allow the notes to automatically convert into shares of common stock at maturity. The amendment was deemed to be a substantive change resulting in a loss on extinguishment of debt with an offsetting premium to the convertible notes.

During September 2015, we amended our outstanding convertible notes to provide that the principal and any accrued and unpaid interest would automatically convert into shares of our common stock upon the occurrence of an equity financing of at least $2.0 million in gross aggregate cash proceeds at a conversion price equal to the applicable fixed conversion price for the notes; provided, however, if the lowest price per share at which our shares of equity securities were sold in such equity financing was less than the applicable fixed conversion price, then the note conversion price would equal 75% of the lowest price per share at which our shares of equity securities were sold. The amendment was deemed to be a substantive change resulting in a loss on extinguishment of debt.

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, 2017, we do not believe any material uncertain tax positions are present.

As of December 31, 2017, we had federal and state net operating loss carryforwards of approximately $61 million which will begin expiring in 2033.

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

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

companies to pay a one-time transition tax on certain unrepatriated earnings of foreign subsidiaries. The impact on our financial statements for the period ended December 31, 2017 is immaterial, primarily because we have a valuation allowance on deferred tax assets in the U.S.

Stock-based compensation

For stock options issued to employees and members of the board of directors for their services, 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 awards expected to vest and account for 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.

For stock-based payments issued to non-employees, compensation expense is determined at the "measurement date," which is the earlier of (i) the date at which a commitment for performance by the counterparty to earn the equity instrument is reached or (ii) the date at which the counterparty's performance is complete. The expense is recognized over the vesting period of the award. Until the measurement date is reached, the total amount of compensation expense remains uncertain. We record compensation expense based on the fair value of the award at the reporting date. The awards to non-employees are then revalued, or the total compensation is recalculated based on the then-current fair value, at each subsequent reporting date.

Results of Operations

Comparison of the Years Ended December 31, 2017 and 2016

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

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

Research and Development Expenses. Our research and development expenses for the year ended December 31, 2017 were $20.0 million, compared to $21.2 million for the year ended December 31, 2016, a decrease of $1.2 million. The decrease was primarily due to the lower costs of our previously initiated clinical trials, offset by the initiation of our ADVANCE-1 study as well as an increase in personnel costs and stock compensation expense. We expect our research and development expenses to decrease modestly in 2018. This decrease will be driven by the pause in screening of our COAST-1 trial and cessation of the CREATE-1 study offset by continued enrollment in our STRIDE-

1 and ADVANCE-1 studies, initiation of a Phase 2 study in smoking cessation for AXS-05 and the initiation of a migraine study for AXS-07.

General and Administrative Expenses. Our general and administrative expenses for the year ended December 31, 2017 were $7.2 million, as compared to $6.3 million for the year ended December 31, 2016, an increase of $0.9 million. The increase was primarily due to higher intellectual property costs, stock compensation expense and placement agent expenses associated with our registered direct offering completed in December 2017. We anticipate that our general and administrative expenses will decrease modestly in 2018.

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

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

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

Comparison of the Years Ended December 31, 2016 and 2015

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015:

	Year ended December 31,	
	2016	**2015**
Operating expenses:		
Research and development	$ 21,199,860	6,776,987
General and administrative	6,343,648	2,419,289
Total operating expenses	27,543,508	9,196,276
Loss from operations	(27,543,508)	(9,196,276)
Interest and amortization of debt discount expense	(132,424)	(736,048)
Tax credit	474,279	—
Change in fair value of warrant liability	—	(108,539)
Change in fair value of embedded derivative liabilities	—	274,800
Loss on extinguishment of debt	—	(2,444,516)
Net loss	$ (27,201,653)	(12,210,579)

Research and Development Expenses. Our research and development expenses for the year ended December 31, 2016 were $21.2 million, compared to $6.8 million for the year ended December 31, 2015, an increase of $14.4 million. The increase was primarily due to the conduct of our CREATE-1, STRIDE-1, and COAST-1 studies, as well as an increase in personnel costs and stock compensation expense.

General and Administrative Expenses. Our general and administrative expenses for the year ended December 31, 2016 were $6.3 million, as compared to $2.4 million for the year ended December 31, 2015, an increase of $3.9 million. The increase was primarily due to external fees associated with operating as a public company, as well as an increase in personnel costs and stock compensation expense.

Interest and Amortization of Debt Discount Expense. Interest and amortization of debt discount expense for the year ended December 31, 2016 was $0.1 million, as compared to $0.7 million for the year ended December 31, 2015, a decrease of $0.6 million. In 2016, the expense was related to interest and the amortization of the debt discount associated with our loan and security agreement with SVB. In 2015, the expense was non-cash interest expense related to our then-outstanding convertible notes.

Tax Credit. During the year ended December 31, 2016, we received the NYC Biotech credit in the amount of $0.5 million related to the research and development expenses of our product candidates. There was no tax credit received during the year ended December 31, 2015.

Change in Fair Value of Warrant Liability. There was no warrant liability recorded during the year ended December 31, 2016. We recorded expense related to the change in fair value of our warrant liability for the year ended December 31, 2015 of $0.1 million.

Change in Fair Value of Embedded Derivative Liabilities. There was no embedded derivative liability recorded during the year ended December 31, 2016. We recorded income related to the change in fair value of our embedded derivative liabilities of $0.3 million for the year ended December 31, 2015.

Loss on Extinguishment of Debt. During the year ended December 31, 2015, we amended the conversion provision in our convertible notes issued from September 2014 through July 2015. The amendment was deemed to be a substantive change resulting in a $2.4 million loss on extinguishment of debt. No notes were outstanding in 2016 and no such adjustment occurred during the year ended December 31, 2016.

Liquidity and Capital Resources

In November 2015, we completed our IPO, in which we sold 5,666,667 shares of common stock at a public offering price 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. The initial tranche of $10.0 million was funded shortly after executing the loan agreement. As discussed elsewhere in this Annual Report on Form 10-K, 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.

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 pursuant to which we may sell shares of our common stock from time to time in an at-the-market offering in October 2017, and completed a registered direct offering priced at the market in December 2017, 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 the Sales Agreement with Leerink, pursuant to which we may sell up to $30 million in shares of our common stock from time to time through Leerink, acting as our sales agent, in one or more at-the-market offerings. Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the Sales Agreement. Gross sales of $0.1 million were made under the Sales Agreement during the year ended December 31, 2017.

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.

At December 31, 2017, we had cash of $34.0 million. We currently anticipate our cash to be sufficient to fund our anticipated operating cash requirements into the third quarter of 2019. 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,		
	2017	2016	2015
Net cash (used in) provided by:			
Operating activities	$ (26,471,652)	$ (21,281,304)	$ (7,438,991)
Investing activities	(9,898)	(104,561)	(20,195)
Financing activities	23,884,176	9,968,102	52,877,631
Net increase (decrease) in cash	$ (2,597,374)	$ (11,417,763)	$ 45,418,445

Operating Activities. Net cash used in operating activities for the year ended December 31, 2017 was $26.5 million as compared to $21.3 million for the year ended December 31, 2016. The increase of $5.2 million in net cash used was primarily related to a reduction in accounts payable and accrued expenses, an increase in general and administrative expenses, which includes $0.2 million in placement agent expense associated with our registered direct offering in December 2017, the change in the fair value of warrants, and interest and amortization of debt issuance costs related to our term loan with SVB.

Net cash used in operating activities for the year ended December 31, 2016 was $21.3 million as compared to $7.4 million for the year ended December 31, 2015. The increase of $13.9 million in net cash used was primarily related to an increase in expenditures for our clinical programs, including our CREATE-1, STRIDE-1, and COAST-1 studies, as well as an increase in general and administrative expenses related to operating as a public company.

Investing Activities. Cash used in investing activities for the purchase of equipment was less than $0.1 million for the year ended December 31, 2017 and $0.1 million for the year ended December 31, 2016. Cash used in investing activities was less than $0.1 million for the year ended December 31, 2015.

Financing Activities. 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 term loan of $0.3 million. Net cash provided by financing activities for the year ended December 31, 2016 was $10.0 million, which consisted of the net proceeds received from the term loan with SVB. Net cash provided by financing activities for the year ended December 31, 2015 was $52.9 million, which included the net proceeds of $45.5 million received from our IPO in November 2015 as well as net proceeds of $7.4 million received from convertible notes issued in 2015.

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, 2017:

(in thousands)	Total	Less than one year	1 - 3 years	3 - 5 years	More than 5 years
Term loan	$10,977,708	$4,055,069	$6,922,639	$ —	$ —
Total contractual obligations	$10,977,708	$4,055,069	$6,922,639	$ —	$ —

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

November 2016 Loan and Security Agreement—Silicon Valley Bank

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

The SVB loan accrues 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 is payable monthly. Following the interest only payment period, we will begin making monthly payments of principal and interest until the maturity date of November 1, 2020. In addition, we are 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 may prepay all, but not less than all, of the SVB loan subject to a prepayment premium of 3.0% of the outstanding principal if prepaid within two years of the effective date of the loan, 2.0% of the outstanding principal if prepaid during the third year of the loan, and 1.0% of the outstanding principal if prepaid after the third year. The term loan 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 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 is being amortized to interest expense over the term of the debt.

Shelf Registration Statement

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. At the time any of the securities covered by the 2016 Shelf Registration Statement are offered for sale, a prospectus supplement will be prepared and filed with the SEC containing specific information about the terms of any such offering.

Off-Balance Sheet Arrangements

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

JOBS Act

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

Recent Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board, or "FASB", issued Accounting Standards Update, or "ASU" No. 2016-02, *Leases (Topic 842)*, which supersedes FASB Topic 840, Leases (Topic 840) and provides principles for the recognition, measurement, presentation and disclosure of leases for both lessees and lessors. The new standard requires lessees to apply a dual approach, classifying leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase by the lessee. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease, respectively. A lessee is also required to record a right-of-use asset and a lease liability for all leases with a term of greater than twelve months regardless of classification. Leases with a term of twelve months or less will be accounted for similarly to existing guidance for operating leases. The standard will be effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted upon issuance. The Company is currently evaluating the potential impact of the new guidance.

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

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

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURE ABOUT MARKET RISK

Interest Rate Risk

We are exposed to market risks in the ordinary course of our business. These market risks are principally limited to interest rate fluctuations. We had cash of $34.0 million as of December 31, 2017. The primary objective of our investment activities is to preserve principal and liquidity while maximizing income without significantly increasing risk. We do not enter into investments for trading or speculative purposes. Due to the short-term nature of our investment portfolio, we do not believe an immediate 10% increase in interest rates would have a material effect on the fair market value of our portfolio, and, accordingly, we do not expect our operating results or cash flows to be materially affected by a sudden change in market interest rates.

Foreign Currency Exchange Risk

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

We do not believe a 10% change in these currencies on December 31, 2017 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, 2017.

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, 2017. 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, 2017, our principal executive officer and principal financial officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable level.

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, 2017. 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, 2017, our internal control over financial reporting was effective based on these criteria.

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

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

ITEM 9B. OTHER INFORMATION.

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE.

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

ITEM 11. EXECUTIVE COMPENSATION.

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

PART IV

ITEM 15. EXHIBITS and FINANCIAL STATEMENT SCHEDULES.

(a)1. Consolidated Financial Statements

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

2. Consolidated Financial Statement Schedules

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

3. Exhibits

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

Axsome Therapeutics, Inc.
Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Axsome Therapeutics, Inc. (the "Company") as of December 31, 2017 and 2016, the related consolidated statements of operations, stockholders' equity (deficit), and cash flows, for each of the three years in the period ended December 31, 2017, 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, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, 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 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 7, 2018

Axsome Therapeutics, Inc.
Consolidated Balance Sheets

	December 31, 2017	December 31, 2016
Assets		
Current assets:		
Cash	$ 34,021,123	$ 36,618,497
Prepaid and other current assets	1,278,418	1,380,560
Total current assets	35,299,541	37,999,057
Equipment, net	68,071	100,730
Other assets	187,952	112,821
Total assets	$ 35,555,564	$ 38,212,608
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 3,435,456	$ 4,081,173
Accrued expenses and other current liabilities	2,679,534	2,820,377
Loan payable, current portion	3,269,346	269,162
Warrant liability	2,791,000	—
Total current liabilities	12,175,336	7,170,712
Loan payable, long-term	6,663,005	9,470,445
Total liabilities	18,838,341	16,641,157
Stockholders' equity:		
Preferred stock, $0.0001 par value per share (10,000,000 shares authorized, none issued and outstanding at December 31, 2017 and December 31, 2016, respectively)	—	—
Common stock, $0.0001 par value per share (150,000,000 shares authorized, 25,492,992 and 19,158,417 shares issued and outstanding at December 31, 2017 and December 31, 2016, respectively)	2,549	1,916
Additional paid-in capital	93,299,517	69,210,986
Accumulated deficit	(76,584,843)	(47,641,451)
Total stockholders' equity	16,717,223	21,571,451
Total liabilities and stockholders' equity	$ 35,555,564	$ 38,212,608

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

Axsome Therapeutics, Inc.
Consolidated Statements of Operations

	Year ended December 31,		
	2017	2016	2015
Operating expenses:			
Research and development	$ 19,957,616	$ 21,199,860	$ 6,776,987
General and administrative	7,206,691	6,343,648	2,419,289
Total operating expenses	27,164,307	27,543,508	9,196,276
Loss from operations	(27,164,307)	(27,543,508)	(9,196,276)
Interest and amortization of debt discount expense	(1,340,199)	(132,424)	(736,048)
Tax credit	207,114	474,279	—
Change in fair value of warrant liability	(646,000)	—	(108,539)
Change in fair value of embedded derivative liabilities	—	—	274,800
Loss on extinguishment of debt	—	—	(2,444,516)
Net loss	$ (28,943,392)	$ (27,201,653)	$ (12,210,579)
Net loss per common share, basic and diluted	$ (1.27)	$ (1.42)	$ (1.02)
Weighted average common shares outstanding, basic and diluted	22,764,606	19,150,690	11,945,318

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

Axsome Therapeutics, Inc.
Consolidated Statements of Stockholders' Equity (Deficit)

	Common stock		Additional paid-in capital	Accumulated deficit	Total stockholders' equity (deficit)
	Shares	Amount			
Balance at December 31, 2014	11,108,144	$ 1,111	$ 5,025,533	$ (8,229,219)	$ (3,202,575)
Stock-based compensation	—	—	803,279	—	803,279
Issuance of common stock in initial public offering, net of expenses	5,666,667	567	45,505,934	—	45,506,501
Issuance of common stock upon conversion of convertible notes	2,374,606	237	15,302,624	—	15,302,861
Reclassification of warrant liability	—	—	244,774	—	244,774
Net loss	—	—	—	(12,210,579)	(12,210,579)
Balance at December 31, 2015	19,149,417	1,915	66,882,144	(20,439,798)	46,444,261
Stock-based compensation	—	—	2,031,418	—	2,031,418
Proceeds from exercise of options	9,000	1	33,029	—	33,030
Issuance of warrants	—	—	264,395	—	264,395
Net loss	—	—	—	(27,201,653)	(27,201,653)
Balance at December 31, 2016	19,158,417	1,916	69,210,986	(47,641,451)	21,571,451
Stock-based compensation	—	—	2,072,210	—	2,072,210
Issuance of common stock upon exercise of options	88,922	9	316,710	—	316,719
Issuance 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

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

Axsome Therapeutics, Inc.
Consolidated Statements of Cash Flows

	Year ended December 31,		
	2017	2016	2015
Cash flows from operating activities			
Net loss	$ (28,943,392)	$ (27,201,653)	$ (12,210,579)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	2,072,210	2,031,418	803,279
Amortization of debt discount	470,521	68,930	42,202
Amortization of debt issuance costs	—	—	7,757
Non-cash interest expense	—	—	698,826
Change in fair value of warrants	646,000	—	108,539
Change in fair value of embedded derivative liabilities	—	—	(274,800)
Loss on extinguishment of debt	—	—	2,444,516
Depreciation	42,557	20,484	3,542
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	102,143	(383,942)	(870,673)
Other assets	(75,131)	(86,196)	(26,625)
Accounts payable	(645,717)	2,188,810	1,134,204
Accrued expenses and other current liabilities	(140,843)	2,080,845	700,821
Net cash used in operating activities	(26,471,652)	(21,281,304)	(7,438,991)
Cash flows from investing activities			
Purchases of equipment	(9,898)	(104,561)	(20,195)
Net cash used in investing activities	(9,898)	(104,561)	(20,195)
Cash flows from financing activities			
Proceeds from issuance of convertible notes	—	—	7,382,468
Proceeds from issuance of term loan	—	10,000,000	—
Payment of debt issuance costs	—	(64,928)	(12,489)
Repayment of principal on term loan	(277,778)	—	—
Proceeds from issuance of initial public offering, net	—	—	45,549,121
Proceeds from issuance of common stock upon financing, net	23,677,341	—	—
Proceeds from issuance of common stock upon exercise of warrants	167,894	33,030	—
Proceeds from issuance of common stock upon exercise of options	316,719	—	—
Payment of loan from related party	—	—	(41,469)
Net cash provided by financing activities	23,884,176	9,968,102	52,877,631
Net (decrease) increase in cash	(2,597,374)	(11,417,763)	45,418,445
Cash at beginning of period	36,618,497	48,036,260	2,617,815
Cash at end of period	$ 34,021,123	$ 36,618,497	$ 48,036,260
Supplemental disclosures of non-cash financing activity:			
Establishment of warrant liabilities in connection with common stock issuance	$ 2,145,000	$ —	$ —
Issuance of warrants in connection with debt financing	$ —	$ 264,395	$ —
Conversion of convertible notes to common stock	$ —	$ —	$ 15,302,861

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, or 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 product candidate portfolio includes five product candidates, AXS-05, AXS-09, AXS-02, AXS-07, and AXS-06, 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

On October 30, 2015, the Company filed an amendment to its Certificate of Incorporation whereby the Company (i) increased the number of authorized shares of common stock to 25,000,000 shares and (ii) effectuated a 7.3445-for-1 forward stock split of its common stock. Fractional shares resulting from the stock split were rounded down to the next whole share and in lieu of any fractional shares the Company will pay a cash amount to the holder of such fractional share equal to the fair market value of such fractional share as determined by the Company's board of directors. The accompanying audited financial statements and notes to the financial statements give retroactive effect to this stock split for all periods presented.

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, 2017, the Company had an accumulated deficit of $76.6 million.

In November 2015, the Company completed its IPO, whereby it sold 5,666,667 shares of common stock at a public offering price of $9.00 per share. The Company received gross proceeds of approximately $51.0 million and net proceeds of approximately $45.5 million, after deducting underwriting discounts and commissions and offering-related transaction costs.

In November 2016, the Company entered into a loan and security agreement with Silicon Valley Bank ("SVB") for a term loan of up to $20.0 million. The initial tranche of $10.0 million was funded shortly after executing the loan agreement. The Company did not achieve the conditional criteria to access the second and third tranches before the specified dates and the $10.0 million in additional term loan advances have expired.

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

In October 2017, the Company entered into a sales agreement (the “Sales Agreement”) with Leerink Partners LLC ("Leerink"), pursuant to which the Company may sell up to $30 million in shares of its common stock from time to time through Leerink, acting as its sales agent, in one or more at-the-market offerings. Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the Sales Agreement. Gross sales of $0.1 million were made under the Sales Agreement during the year ended December 31, 2017.

In December 2017, the Company completed a registered direct offering priced at the market, whereby it sold 1,783,587 shares of common stock and warrants to purchase up to an aggregate of 1,783,587 shares of its common stock at a combined purchase price of $5.325 per share. The Company received gross proceeds of approximately $9.5 million and net proceeds of approximately $8.8 million, net of underwriting discounts and offering expenses.

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.

As of December 31, 2017, the Company had $34.0 million in cash. The Company currently anticipates its cash to be sufficient to fund its anticipated operating cash requirements into the third quarter of 2019. The actual amount of cash that the Company will need to operate is subject to many factors, including, but not limited to, the timing, design and conduct of clinical trials for its product candidates. The Company is dependent upon significant future financing to provide the cash necessary to execute its current operations, including the commercialization of any of its product candidates.

The Company’s common stock is listed on the Nasdaq Global Market and trades under the symbol “AXSM”.

Note 2. Summary of Significant Accounting Policies

Significant Risks and Uncertainties

The Company’s operations are subject to a number of factors that can affect its operating results and financial condition. Such factors include, but are not limited to: the results of clinical testing and trial activities of the Company’s product candidates; the Company’s ability to obtain regulatory approval to market its products, if approved; competition from products manufactured and sold or being developed by other companies; the price of, and demand for, Company products, if approved; the Company’s ability to negotiate favorable licensing or other manufacturing and marketing agreements for its products, if approved; and the Company’s ability to raise additional financing. If the Company does not successfully commercialize any of its product candidates, it will be unable to generate recurring product revenue or achieve and maintain profitability.

Use of Estimates

Management considers many factors in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. This process may

result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. In preparing these financial statements, management used significant estimates in the following areas, among others: stock-based compensation expense; the determination of the fair value of the warrant and embedded derivative liabilities; the accounting for research and development costs; and the recoverability of the Company's net deferred tax assets and related valuation allowance.

Prior to being a public company, the Company utilized significant estimates and assumptions in determining the fair value of its common stock. The Company granted stock options at exercise prices not less than the fair market value of its common stock as determined by the board of directors, with input from management. The board of directors determined the estimated fair value of the Company's common stock based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry, the prices at which the Company issued convertible notes, and the likelihood of achieving a liquidity event, such as an IPO or sale of the Company.

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, 2017 and 2016.

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, 2017, the majority of the Company's cash was held by one financial institution and the amount on deposit was in excess of Federal Deposit Insurance Corporation insurance limits. The Company has not recognized any losses from credit risks on such accounts since inception. The Company believes it is not exposed to significant credit risk on cash.

Fair Value of Financial Instruments

Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants at the measurement date. Assets and liabilities that are measured at fair value are reported using a three-level fair value hierarchy that prioritizes the inputs used to measure fair value. This hierarchy maximizes the use of observable inputs and minimizes the use of unobservable inputs. The three levels of inputs used to measure fair value are as follows:

Level 1—Quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Inputs other than quoted prices in active markets that are observable for the asset or liability, either directly or indirectly.

Level 3—Inputs that are unobservable for the asset or liability.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying amounts reported in the accompanying consolidated financial statements for accounts payable and accrued expenses approximate their respective fair values due to their short-term maturities. The fair value of the warrant and embedded derivative liabilities are discussed in Note 3, "Fair Value Measurements."

Debt Issuance Costs

The Company incurred third-party costs in connection with the Company's convertible notes and term loan as described in Note 6 and Note 7, respectively. 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, 2017, 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 to employees and members of the Company's board of directors for their services, 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 awards expected to vest and accounts for 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.

For stock-based payments issued to non-employees, compensation expense is determined at the "measurement date," which is the earlier of (i) the date at which a commitment for performance by the counterparty to earn the equity instrument is reached or (ii) the date at which the counterparty's performance is complete. The expense is recognized over the vesting period of the award. Until the measurement date is reached, the total amount of compensation expense remains uncertain. The Company records compensation expense based on the fair value of the award at the reporting date. The awards to non-employees are then revalued, or the total compensation is recalculated based on the then-current fair value, at each subsequent reporting date.

Tax Credit

The tax credit represents the receipt of the New York City Biotechnology Tax Credit, or NYC Biotech credit, and receipt by Axsome Therapeutics Australia PTY, LTD, our Australian subsidiary, of the Australia Tax Incentive Credit, related to our research and development expenses incurred for our 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, 2017, 2016, and 2015.

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) and provides principles for the recognition, measurement, presentation and disclosure of leases for both lessees and lessors. The new standard requires lessees to apply a dual approach, classifying leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase by the lessee. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease, respectively. A lessee is also required to record a right-of-use asset and a lease liability for all leases with a term of greater than twelve months regardless of classification. Leases with a term of twelve months or less will be accounted for similarly to existing guidance for operating leases. The standard will be effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted upon issuance. The Company is currently evaluating the potential impact of the new guidance.

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

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

Note 3. Fair Value Measurements

2017 Warrants associated with Registered Direct Offering

In accordance with *ASC820, Fair Value Measurements and Disclosures*, financial instruments were measured at fair value using a three-level hierarchy which maximizes use of observable inputs and minimizes use of unobservable inputs:

Level 1—Quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Inputs other than quoted prices in active markets that are observable for the asset or liability, either directly or indirectly.

Level 3—Inputs that are unobservable for the asset or liability.

In connection with the Company's December 4, 2017 registered direct offering (the "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 are exercisable at $5.25 per share and expire on December 11, 2018. Additionally, as part of the 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 Registered Direct Offering to purchase an aggregate of 107,015 shares of its common stock. The Placement

Agent Warrants are exercisable at $6.6562 and expire on December 11, 2018. The Common Warrants and Placement Agent Warrants were analyzed and it was determined that they require liability treatment. Under ASC 815, registered common stock warrants that require the issuance of registered shares upon exercise and do not expressly preclude an implied right to cash settlement are accounted for as derivative liabilities. The Company classifies these derivative warrant liabilities on the consolidated balance sheet as a current liability.

The fair value of the Common Warrants at December 4, 2017, the date these warrants were issued, and December 31, 2017 were determined to be approximately $2,064,000 and $2,683,000, respectively, as calculated using Black-Scholes with the following assumptions: (1) stock price of $5.00 and $5.60, respectively; (2) a risk-free rate of 1.66% and 1.76%, respectively; and (3) an expected volatility of 61% and 62%, respectively. The fair value of the Common Warrants were reported as a warrant liability on the balance sheet and the change in the fair value between December 4, 2017 and December 31, 2017 is reported as a change in fair value of the warrant liability on the statement of operations.

The fair value of the Placement Agent Warrants at December 4, 2017, the date these warrants were issued, and December 31, 2017 were determined to be approximately $81,000 and $108,000, respectively, as calculated using Black-Scholes with the following assumptions: (1) stock price of $5.00 and $5.60, respectively; (2) a risk-free rate of 1.66% and 1.76%, respectively; and (3) an expected volatility of 61% and 62%, respectively. The fair value of the Placement Agent Warrants were reported as a warrant liability on the balance sheet and the change in the fair value between December 4, 2017 and December 31, 2017 is reported as a change in fair value of the warrant liability on the statement of operations.

Level 3 Fair Value Sensitivity

Warrant liability

As of December 31, 2017, the fair value of the warrant liability utilizes inputs including: share price, expected volatility and risk-free rate.

- A 10% plus/minus change in share price will result in an estimated increase/decrease of $0.7 million in the value of the warrant liability,
- A 10% plus/minus change in the expected volatility will result in an estimated increase/decrease of $0.2 million in the value of the warrant liability, and
- A 10% plus/minus change in the risk-free interest rate will result in an immaterial change in the value of the warrant liability.

There were no financial liabilities measured at fair value on a recurring basis as of December 31, 2016 and 2015.

The following table sets forth a summary of changes in the fair value of Level 3 liabilities for the years ended December 31, 2017, 2016, and 2015:

December 31, 2017	Beginning of period	Issuances	Change in fair value (3)	Extinguishments	End of period
Warrant liability	$ —	$ 2,145,000	$ 646,000	$ —	$ 2,791,000
Embedded derivative liabilities	—	—	—	—	—
Total	$ —	$ 2,145,000	$ 646,000	$ —	$ 2,791,000

December 31, 2016	Beginning of period	Issuances	Change in fair value (3)	Extinguishments	End of period
Warrant liability	$ —	$ —	$ —	$ —	$ —
Embedded derivative liabilities	—	—	—	—	—
Total	$ —	$ —	$ —	$ —	$ —

December 31, 2015	Beginning of period	Issuances	Change in fair value (3)	Extinguishments	End of period
Warrant liability (1)	$ 136,235	$ —	$ 108,539	$ (244,774)	$ —
Embedded derivative liabilities (2)	496,400	871,000	(274,800)	(1,092,600)	—
Total	$ 632,635	$ 871,000	$ (166,261)	$ (1,337,374)	$ —

(1) Prior to the close of the Company's IPO on November 24, 2015, the Company considered its convertible note related warrant liability as a Level 3 financial instrument. On the grant date and in subsequent periods, the Company estimated the fair value of the warrant liability using the Black-Scholes option pricing model, which requires inputs such as the expected volatility based on comparable public companies, the estimated fair value of the common stock, and the estimated time to liquidity. The Company determined the fair value of the liability immediately prior to the Company's IPO and then reclassified the balance to additional paid-in capital upon the closing of the IPO. Immediately prior to the close of the Company's IPO, the following inputs were used for the warrant liability:

	Immediately prior to close of IPO
Expected volatility based on comparable public companies	70 %
Estimated fair value of the common stock	$ 9.20
Remaining contractual term	4 years

(2) Prior to the amendment of the Company's outstanding convertible notes in September 2015, the Company considered its convertible note related embedded derivative liabilities as Level 3 financial instruments. The fair value of the embedded derivative liabilities related to the Company's outstanding convertible notes was estimated on the grant date and at each reporting period using a probability weighted estimated returns method, which incorporated the "with-and-without" method to bifurcate the embedded derivatives. The amendment was deemed to be a substantive change and resulted in extinguishment accounting, which included the extinguishment of the embedded derivative liabilities. The Company used three different exit scenarios in valuing the embedded derivative liabilities: an initial public offering, a private equity financing, and a liquidation. A Monte Carlo simulation was run for the exit scenario immediately prior to the effective date of the note amendment, with the following inputs:

	Immediately prior to note amendment
Expected volatility based on comparable public companies	70 %
Estimated time to liquidity	0.1 - 0.2 years

(3) The change in the fair values of the warrant and embedded derivative liabilities are recorded in the statements of operations.

Note 4. Net Loss per Common Share

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

	Year ended December 31,		
	2017	2016	2015
Basic and diluted net loss per common share:			
Net loss	$ (28,943,392)	$ (27,201,653)	$ (12,210,579)
Weighted average common shares outstanding—basic and diluted	22,764,606	19,150,690	11,945,318
Net loss per common share—basic and diluted	$ (1.27)	$ (1.42)	$ (1.02)

The following potentially dilutive securities outstanding at December 31, 2017, 2016, and 2015 have been excluded from the computation of diluted weighted average shares outstanding, as they would be anti-dilutive:

	December 31,		
	2017	2016	2015
Stock options	2,315,638	1,772,050	998,198
Warrants	2,099,149	337,696	272,468
	4,414,787	2,109,746	1,270,666

Note 5. Accrued Expenses

At December 31, 2017 and 2016, accrued expenses consisted of the following:

	December 31, 2017	December 31, 2016
Research and development	$ 1,642,154	$ 1,693,748
Accrued compensation	704,556	539,290
Other	332,824	587,339
	$ 2,679,534	$ 2,820,377

Note 6. Convertible Notes

During March 2013, the Company issued a total of $211,000 in convertible notes (“March 2013 Notes”) to several investors. The March 2013 Notes accrued interest at an annual rate of 8.0% and were due and payable one year from the date of issuance. The principal and accrued interest were convertible into shares of the Company’s common stock at the option of the holder, upon the occurrence of a qualified financing, as defined in the March 2013 Notes, immediately prior to the closing of a change in control event, or on the maturity date. In March 2014, all outstanding March 2013 Notes and related accrued interest converted into 175,228 shares of common stock at a conversion price of $1.30 per share.

During the period from June through October 2013, the Company issued a total of $3,904,000 in convertible notes to several investors (“June 2013 Notes”). The June 2013 Notes accrued interest at an annual rate of 8.0% and were due and payable one year from the date of issuance. The principal and accrued interest were convertible into shares of the Company’s common stock at the option of the holder, or upon the occurrence of a qualified financing, as defined in the June 2013 Notes, in which the conversion price would be equal to the lesser of (i) 90% of the lowest price per share at which the Company’s shares of equity securities were sold or (ii) $1.30, as adjusted for capitalization change. The Company recorded an initial discount on the June 2013 Notes of $339,735 for fees paid directly to the placement agent.

In June 2014, the Company and the holders of the June 2013 Notes amended the June 2013 Notes pursuant to which the June 2013 Notes and any accrued and unpaid interest would convert into shares of the Company’s common stock on the due date at a conversion price of $1.30 (see further discussions in “—Accounting Analysis” below). In accordance with this amendment, during the period from June 2014 through October 2014, all of the outstanding balance of the June 2013 Notes and accrued and unpaid interest converted into 3,242,344 shares of common stock.

During the period from September 2014 through November 2014, the Company issued a total of $4,140,000 in convertible notes to several investors (“September 2014 Notes”). The September 2014 Notes accrued interest at an annual rate of 8.0% and were due and payable ten years from the date of issuance. The principal and accrued interest were convertible into shares of the Company’s common stock upon the occurrence of a qualified financing, as defined in the September 2014 Notes, in which the conversion price would be equal to the lesser of (i) 75% of the lowest price per share at which the Company's shares of equity securities are sold (see further discussions in “—Accounting Analysis” below), or (ii) $5.40, as adjusted for capitalization change. The Company’s IPO in November 2015 met the definition of a qualified financing, and upon the close of the IPO all of the outstanding balance of the September 2014 Notes and accrued and unpaid interest converted into 836,202 shares of common stock.

During the period from December 2014 through January 2015, the Company issued a total of $1,570,000 in convertible notes to several investors (“December 2014 Notes”). The December 2014 Notes accrued interest at an annual rate of 8.0% and were due and payable ten years from the date of issuance. The principal and accrued interest were convertible into shares of the Company’s common stock upon the occurrence of a qualified financing, as defined in the December 2014 Notes, in which the conversion price would be equal to the lesser of (i) 75% of the lowest price per share at which the Company's shares of equity securities are sold (see further discussions in “—Accounting Analysis” below), or (ii) $5.94, as adjusted for capitalization change. The Company’s IPO in November 2015 met the definition of a qualified financing, and upon the close of the IPO all of the outstanding balance of the December 2014 Notes and accrued and unpaid interest converted into 283,131 shares of common stock.

During the period from May 2015 through July 2015, the Company issued a total of $7,166,469 in convertible notes (“2015 Notes”). The 2015 Notes accrued interest at an annual rate of 8.0% and were due and payable ten years from the date of issuance. The principal and accrued interest were convertible into shares of the Company’s common stock upon the occurrence of a qualified financing, as defined in the 2015 Notes, in which the conversion price would be equal to the lesser of (i) 75% of the lowest price per share at which the Company's shares of equity securities are sold (see further discussions in “—Accounting Analysis” below), or (ii) $5.94, as adjusted for capitalization change. The Company’s IPO in November 2015 met the definition of a qualified financing, and upon the close of the IPO all of the outstanding balance of the 2015 Notes and accrued and unpaid interest converted into 1,255,273 shares of common stock.

In September 2015, the Company and the holders of its outstanding convertible notes amended the terms of the September 2014 Notes, December 2014 Notes, and 2015 Notes to provide that the principal and any accrued and unpaid interest would automatically convert into shares of the Company’s common stock upon the occurrence of an equity financing of at least $2.0 million in gross aggregate cash proceeds at a conversion price equal to the applicable fixed conversion price for the notes; provided, however, if the lowest price per share at which the shares of equity securities were sold in such equity financing is less than the applicable fixed conversion price, then the note conversion price would equal 75% of the lowest price per share at which the shares of equity securities are sold (see further discussions in “—Accounting Analysis” below).

Accounting Analysis

The June 2014 amendment of the June 2013 Notes, pursuant to which the June 2013 Notes plus any accrued and unpaid interest automatically converted into shares of the Company’s common stock on the due date, was considered substantive. As such, the June 2013 Notes were considered extinguished, and the amended notes were recorded at fair value. The difference between the fair value of the amended notes of $6,691,000, which was measured using the backsolve method, and the carrying value of the extinguished notes of $3,820,097 was recorded as a loss on extinguishment of debt in the Company’s consolidated financial statements. The difference between the fair value and the face value of the amended notes was recorded as a premium to the notes and amortized over the remaining life of the notes. The amortization of the premium is included in interest and amortization of debt discount/premium (expense) income in the consolidated statements of operations.

The September 2014 Notes, December 2014 Notes, and 2015 Notes each included a redemption provision, which is an embedded derivative. These embedded derivatives required bifurcation from the host debt instrument. The Company aggregated these bifurcated features and reflected the values of these embedded derivatives in the account “embedded derivative liabilities” that was re-measured at each reporting period and any changes in fair value was recognized in the consolidated statements of operations. See Note 3, “Fair Value Measurements.”

The September 2015 amendment to the September 2014 Notes, December 2014 Notes, and 2015 Notes amended the conversion provision, which was considered substantive. As such, the September 2014 Notes, December 2014 Notes, and 2015 Notes were considered extinguished, and the amended notes were recorded at fair value. The difference between the fair value of the amended notes of $15,146,410 and the carrying value of the extinguished notes of $12,701,894 was recorded as a loss on extinguishment of debt in the Company’s consolidated financial statements.

No convertible notes were outstanding as of December 31, 2017, 2016 and 2015.

Note 7. Loan and Security Agreement

In November 2016, the Company entered into a $20.0 million Term Loan Agreement ("Term Loan") with SVB. The three-tranche Term Loan consists of an initial $10.0 million tranche triggered upon closing, with the remaining $10.0 million available to be drawn in two $5.0 million tranches, at the Company's option, subject to the achievement of certain clinical and financial milestones.

The loan bears 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 is payable monthly. It matures in November 2020 and has an interest-only payment period until December 1,2017, which may be extended to May 2018 upon the drawing of the second tranche. Following the interest only payment period, the Company will begin making monthly payments of principal and interest 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 is required to pay a final payment fee of 8.5% of the principal amount extended on the date of repayment of the Term Loan, which is being accreted and amortized into interest expense using the effective interest rate method over the term of the loan. Because the Company did not achieve the conditional criteria to access the second and third term advances before the specified dates, the $10.0 million in additional term loan advances expired and the Company began to repay principal in December 2017.

The Company may prepay all, but not less than all, of the 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 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.

Interest expense was $869,678 and $116,736 and amortization of the final payment was $346,978 and $49,781 for the years ended December 31, 2017 and 2016, respectively.

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

	December 31, 2017
Long-term debt	$ 9,722,222
Less debt discount, net of current portion	274,116
Long-term debt, net of debt discount	9,996,338
Less current portion of long-term debt	(3,333,333)
Loan payable, long-term	$ 6,663,005
Current portion of long-term debt	3,333,333
Current portion of debt discount	(63,987)
Loan payable, current portion	$ 3,269,346

In connection with the Term Loan, SVB and Life Science Loans, LLC ("the lenders") received warrants to purchase an aggregate 65,228 shares of the Company's common stock at an exercise price of $7.41 per share, which are exercisable for seven years from the date of issuance.

The proceeds of $10.0 million were allocated based on the relative fair values of the debt instrument and the warrant instrument. The fair value of the warrants and the closing costs were recorded as debt discounts and are being amortized using the effective interest rate method over the term of the loan. Amortization of the debt discount was $123,543 and $19,149 for the years ended December 31, 2017 and 2016, respectively.

Scheduled principal payments on outstanding debt, as of December 31, 2017, are as follows:

2018	$ 3,333,333
2019	3,333,333
2020	3,055,556
	$ 9,722,222

Note 8. Stockholders' Equity

Capital Structure

As of December 31, 2014, the Company was authorized to issue 14,689,000 shares of common stock at $0.0001 par value per share. In April 2015, the Company's board of directors and stockholders approved an increase of the Company's authorized shares of common stock to 22,033,500 shares. In connection with the close of the Company's IPO on November 24, 2015, the Company's stockholders approved an amended and restated certificate of incorporation increasing the number of authorized shares of common stock to 150,000,000 and the number of authorized shares of preferred stock to 10,000,000, par value $0.0001 per share.

In November 2015, the Company completed its IPO, whereby it sold 5,666,667 shares of common stock at a public offering price of $9.00 per share. The Company received gross proceeds of approximately $51.0 million and net proceeds of approximately $45.5 million, after deducting underwriting discounts and commissions and offering-related transaction costs.

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

In October 2017, the Company entered into the Sales Agreement with Leerink , pursuant to which the Company may sell up to $30 million in shares of its common stock from time to time through Leerink, acting as its sales agent, in one or more at-the-market offerings. Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the Sales Agreement. Gross sales of $0.1 million were made under the Sales Agreement during the year ended December 31, 2017.

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.

Each of the warrants issued in December 2017, in connection with the Registered Direct Offering are liabilities pursuant to ASC 815 as registered common stock warrants that require the issuance of registered shares upon exercise and do not expressly preclude an implied right to cash settlement are accounted for as derivative liabilities. The Company classifies these derivative warrant liabilities on the consolidated balance sheet as a current liability. The initial fair value of the Common Warrants and Placement Agent Warrants was estimated to be approximately $2,145,000 and was deducted from the gross proceeds of the Unit offering with the residual amount recorded to equity.

The holders of shares of common stock are entitled to one vote for each share of common stock held at all meetings of stockholders and written actions in lieu of meetings. The holders of shares of common stock are entitled to receive dividends, if and when declared by the board of directors.

Shelf Registration Statement

On December 1, 2016, the Company filed a shelf registration statement with the Securities and Exchange Commission ("SEC") for the issuance of common stock, preferred stock, warrants, rights, debt securities and units up to an aggregate amount of $150.0 million, which the Company refers to as the 2016 Shelf Registration Statement. On December 16, 2016, the 2016 Shelf Registration Statement was declared effective by the SEC. The Company completed an offering of common stock in March 2017, entered into a sales agreement in October 2017 pursuant to which the Company may sell shares of its common stock from time to time in an at-the-market offering and sold shares of its common stock and warrants (as described above) in the Registered Direct Offering priced at the market in December 2017 utilizing the 2016 Shelf Registration Statement. In the future, the Company may also periodically offer one or more of these securities in amounts, prices and terms to be announced when and if the securities are offered. At the time any of the securities covered by the 2016 Shelf Registration Statement are offered for sale, a prospectus supplement will be prepared and filed with the SEC containing specific information about the terms of any such offering.

Equity Incentive Plans

The Company had granted stock options under its 2013 Equity Compensation Plan (the "2013 Plan"), which was adopted for employees and consultants for the purpose of advancing the interests of the Company's stockholders by enhancing its ability to attract, retain and motivate persons who are expected to make important contributions to the Company. In November 2015, the 2015 Omnibus Incentive Compensation Plan (the "2015 Plan") was adopted by the Company's stockholders. The 2015 Plan is the successor to the Company's 2013 Plan. In conjunction with the adoption of the 2015 Plan, no additional grants were made from the 2013 Plan and options from the 2013 Plan remain outstanding. As of December 31, 2017, there were 2,852,551 shares available for future grant under the 2015 Plan.

Stock Options

The following table summarizes stock option activity as of December 31, 2017:

	Number of shares	Weighted average exercise price	Weighted average contractual term	Aggregate intrinsic value
Outstanding at December 31, 2016	1,772,050	$ 5.74		
Granted	847,510	5.24		
Exercised	(88,922)	3.56		
Forfeited	(101,497)	6.69		
Expired	(113,503)	6.30		
Outstanding at December 31, 2017	2,315,638	$ 5.57	8.2	$ 2,385,761
Vested and expected to vest at December 31, 2017	2,309,469	$ 5.58	8.2	$ 2,359,235
Exercisable at December 31, 2017	1,190,135	$ 4.78	7.5	$ 2,042,324

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option pricing model. The Company periodically remeasures the fair value of stock-based awards issued to non-employees and records the expense over the requisite service period. 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, 2017, 2016 and 2015 is as follows:

Black-Scholes option valuation assumptions	2017	2016	2015
Risk-free interest rates	1.6 - 2.2 %	0.9 - 2.0 %	0.7 - 1.9 %
Dividend yield	—	—	—
Volatility	73 - 77 %	69 - 75 %	67 - 71 %
Weighted average expected term	3.50 - 6.12 years	3.25 - 6.25 years	2.5 - 6 years

The weighted average valuation date fair value of options granted was $3.06, $5.13, and $4.21 per option for the years ended December 31, 2017, 2016 and 2015, respectively. As of December 31, 2017, there was $4.1 million of total unrecognized compensation cost related to non-vested stock options which is expected to be recognized over a weighted average period of 2.7 years. These amounts do not include 47,153 options outstanding as of December 31, 2017, 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, 2017, 2016 and 2015 was as follows:

	2017	2016	2015
Research and development	$ 613,629	$ 1,115,626	$ 622,901
General and administrative	1,458,581	915,792	180,378
	$ 2,072,210	$ 2,031,418	$ 803,279

Performance-Based Awards

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. The Company issued no performance-based awards during the year ended December 31, 2016. During the year ended December 31, 2015, the Company issued 81,346 options with a weighted average exercise price of $6.47, to employees and non-employees that vest upon the completion of certain clinical and corporate 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, 2017, 2016, and 2015, the Company recognized $59,424, $604,866, and $283,394, respectively, as expense related to performance-based awards.

Note 9. Warrants

As of December 31, 2017, the Company had outstanding warrants to purchase 2,099,149 shares of common stock. The following table summarizes warrant activity as of December 31, 2017, 2016 and 2015:

	Warrants	Weighted average exercise price
Outstanding at December 31, 2014	230,409	$ 1.30
Issued	42,059	5.94
Outstanding at December 31, 2015	272,468	2.02
Issued	65,228	7.41
Outstanding at December 31, 2016	337,696	3.06
Issued	1,890,602	5.33
Exercised	(129,149)	1.30
Outstanding at December 31, 2017	2,099,149	$ 5.21

In connection with the the Registered Direct Offering, 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. The Common Warrants and Placement Agent Warrants were classified as warrant liabilitity. See Note 3, “Fair Value Measurements”, for the fair value calculations of the warrant liability.

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. The warrants were classified as a component of stockholders' equity.

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 the September 2014 Notes, which were exercisable upon issuance. The warrants were initially classified as a liability in the consolidated financial statements, as upon a qualified financing, as defined in the September 2014 Notes, 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. See Note 3, “Fair Value Measurements”, for the fair value calculations of the warrant liability.

On October 29, 2013, the Company issued warrants to purchase 230,409 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. The warrants were classified as a component of stockholders’ equity.

The value of the warrants issued in 2016 of $264,365 was determined using the Black-Scholes option-pricing model with the following assumptions:

Black-Scholes option valuation assumptions	2016
Risk-free interest rate	1.8 %
Dividend yield	—
Volatility	73 %
Weighted average contractual term	7 years

Note 10. License Agreements

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

Note 11. Commitments and Contingencies

Operating Leases

The Company's offices are located in New York, New York. The Company is not currently under a lease agreement. Rent expense incurred during the years ended December 31, 2017, 2016 and 2015 was $307,557, $254,170, and $127,559.

Note 12. Income Taxes

As of December 31, 2017, the Company had U.S. net operating loss ("NOL") carryforwards of $61 million, which will expire beginning in 2033. The NOL carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. NOL carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders, as defined under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, as well as similar state tax provisions. This could limit the amount of NOLs that the Company can utilize annually to offset future taxable income or tax liabilities.

The components of the Company's deferred tax assets are as follows:

	December 31, 2017	December 31, 2016
Deferred tax assets:		
Net federal operating loss carryforward	$ 12,844,032	$ 12,747,837
Net foreign operating loss carryforward	49,846	23,293
Net state operating loss carryforward	7,981,812	4,068,086
Non-cash compensation	1,719,315	1,450,620
Research and development credits	5,713,709	3,491,251
Deferred finance costs	44,042	—
Fixed Assets	2,597	—
Accrued expenses	472,004	308,007
Deferred tax asset, excluding valuation allowance	28,827,357	22,089,094
Fixed Assets	—	(19,985)
Less valuation allowance	(28,827,357)	(22,069,109)
Net deferred tax assets	$ —	$ —

The Company records a valuation allowance to reduce the deferred tax assets reported if, based on the weight of available evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a full valuation allowance against its deferred tax assets at December 31, 2017 and 2016 because the Company's management has determined that it is more likely than not that these assets will not be realized. The valuation allowance for deferred tax assets was $7,756,147 as of December 31, 2015.

A reconciliation of income tax expense (benefit) at the statutory federal income tax rate and income taxes as reflected in the consolidated financial statements is as follows:

	December 31, 2017	December 31, 2016
U.S. federal statutory income tax rate	34.0 %	34.0 %
State taxes, net of federal benefit	10.0	9.4
Permanent differences	(2.9)	(3.7)
Tax credit	7.7	12.8
US Federal tax rate change - tax reform	(25.4)	—
Change in valuation allowance	(23.4)	(52.5)
Other	—	—
Effective tax rate	— %	— %

The Company is not currently under examination at the federal or state levels and as of the date of the consolidated financial statements there were no known assessments.

Impact of U.S. Tax Reform

On December 22, 2017, the U.S. President signed the Tax Cuts and Jobs Act (the "Act") into law. Effective January 1, 2018, among other changes, the Act (1) reduces the Company's U.S. federal corporate tax rate from 34

percent to 21 percent, (2) changes the rules relating to net operating loss ("NOL") carryforwards and carrybacks, (3) eliminates the corporate alternative minimum tax ("AMT") and changes how existing AMT credits can be realized; and (4) requires companies to pay a one-time transition tax on certain unrepatriated earnings of foreign subsidiaries. The impact on the Company's financial statements for the period ended December 31, 2017 is immaterial, primarily because the Company has a valuation allowance on deferred tax assets in the U.S. In addition, the Act makes the AMT credit refundable in tax years beginning after 2017.

The SEC staff issued Staff Accounting Bulletin ("SAB") 118, which provides guidance on accounting for the tax effects of the Tax Act. SAB 118 provides a measurement period that should not extend beyond one year from the Tax Act enactment date for companies to complete the accounting under Accounting Standards Codification (ASC) 740. In accordance with SAB 118, a company must reflect the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 is complete. To the extent that a company's accounting for certain income tax effects of the Tax Act is incomplete but it is able to determine a reasonable estimate, it must record a provisional estimate in the financial statements. If a company cannot determine a provisional estimate to be included in the financial statements, it should continue to apply ASC 740 on the basis of the provisions of the tax laws that were in effect immediately before the enactment of the Tax Act.

The Tax Act did not have a material impact on our financial statements since our deferred temporary differences in the United States are fully offset by a valuation allowance and we do not have any significant off shore earnings from which to record the mandatory transition tax.

Note 13. Related Party Transactions

From March 2013 through June 2015, members of the Company's board of directors, officers, and some family members participated in the Company's issuance of convertible notes for a total investment of $3,371,469. The terms of these convertible notes were identical to the terms of the convertible notes issued to unrelated third parties. As of December 31, 2015, the entire principal plus interest under these convertible notes issued to these related parties have converted into 696,221 shares of the Company's common stock.

In April 2012, the Company entered into a three-year consulting agreement with Mark Coleman, M.D., a member of its board of directors since December 2014, which was subsequently amended in June 2014, to engage Dr. Coleman to provide certain consulting services in connection with the Company's development of pharmaceutical and other therapeutic product candidates. The consulting agreement provided the Company with the ability to compensate Dr. Coleman in cash or options. In March 2013, the Company issued to Dr. Coleman an option grant to purchase 20,997 shares of the Company's common stock with an exercise price of $1.30 per share that vested immediately; in June 2014, the Company issued to Dr. Coleman an option grant to purchase 76,904 shares of the Company's common stock with an exercise price of $1.30 per share which were subject to certain performance-based vesting restrictions, of which the grant was forfeited in December 2015; and in June 2015, the Company issued to Dr. Coleman an option grant to purchase 33,410 shares of the Company's common stock with an exercise price of $5.94 per share that vested immediately. The Company recorded stock-based compensation expense of $99,234 during the year ended December 31, 2015 related to these option grants. No further expense will be incurred related to these grants.

In 2013, the Company had an outstanding loan payable to its Chief Executive Officer and Chairman of the Board in the amount of $62,469 pertaining to payment of startup costs of the Company. The loan carried no interest payable and was payable on demand. In December 2014, the Company satisfied a portion of the loan payable with a cash payment of $21,000, leaving a balance at December 31, 2014 of $41,469. In June 2015, the Company paid the remaining balance of the loan obligation, which Dr. Tabuteau then reinvested into the Company by purchasing an equivalent amount of convertible notes issued by the Company.

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 10 for further information regarding the license agreements.

Note 14. Quarterly Consolidated Financial Data (Unaudited)

	2017			
	Mar. 31	June 30	Sept. 30	Dec. 31
Total operating expenses	$ 7,672,033	$ 6,750,738	$ 6,297,416	$ 6,444,120
Net loss	$ (7,995,039)	$ (7,084,316)	$ (6,433,536)	$ (7,430,501)
Net loss per common share, basic and diluted (1)	$ (0.41)	$ (0.30)	$ (0.27)	$ (0.31)

	2016			
	Mar. 31	June 30	Sept. 30	Dec. 31
Total operating expenses	$ 5,882,865	$ 6,827,280	$ 7,207,803	$ 7,625,560
Net loss	$ (5,865,941)	$ (6,812,190)	$ (7,194,584)	$ (7,328,938)
Net loss per common share, basic and diluted (1)	$ (0.31)	$ (0.36)	$ (0.38)	$ (0.38)

(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.

INDEX OF EXHIBITS

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation of the Company (Incorporated by reference, Exhibit 3.1 to the Company's Form 8-K (No. 001-37635) filed November 24, 2015.)
3.2	Amended and Restated Bylaws of the Company (Incorporated by reference, Exhibit 3.2 to the Company's Form 8-K (No. 001-37635) filed November 24, 2015.)
4.1	Specimen Certificate evidencing shares of Company's common stock (Incorporated by reference, Exhibit 4.1 to Amendment No. 1 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 30, 2015.)
4.2	Form of warrant to purchase shares of Company's common stock issued in 2013 (Incorporated by reference, Exhibit 4.2 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
4.3	Form of warrant to purchase shares of Company's common stock issued in 2014 (Incorporated by reference, Exhibit 4.3 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
4.4	Warrant Agreement between Axsome Therapeutics, Inc. and Silicon Valley Bank, dated November 9, 2016 (Incorporated by reference, Exhibit 4.1 to the Company's Current Report on Form 8-K filed November 10, 2016.)
4.5	Warrant Agreement between Axsome Therapeutics, Inc. and Life Sciences Loans, LLC, dated November 9, 2016 (Incorporated by reference, Exhibit 4.2 to the Company's Current Report on Form 8-K filed November 10, 2016.)
4.6	Form of Warrant (Incorporated by reference, Exhibit 4.1 to the Company's Current Report on Form 8-K filed December 4, 2017.)
10.1+	Axsome Therapeutics, Inc. 2013 Equity Compensation Plan and Form of Nonqualified Stock Option Agreement thereunder (Incorporated by reference, Exhibit 10.1 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
10.2+	Axsome Therapeutics, Inc. 2015 Omnibus Incentive Compensation Plan (Incorporated by reference, Exhibit 10.6 to Amendment to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 30, 2015.)
10.3+	Axsome Therapeutics, Inc. Form of Stock Option Agreement pursuant to the 2015 Omnibus Incentive Compensation Plan (Incorporated by reference, Exhibit 99.2 to the Company's Registration Statement on Form S-8 (No. 333-208579) filed December 16, 2015.)
10.4*	License Agreement, dated January 12, 2012, by and between the Company and Antecip Bioventures II LLC, as modified by the First Amendment to License Agreement, dated August 21, 2015, by and between the Company and Antecip Bioventures II LLC (Incorporated by reference, Exhibit 10.2 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
10.5*	License Agreement, dated April 17, 2012, by and between the Company and Antecip Bioventures II LLC, as modified by the First Amendment to License Agreement, dated August 21, 2015, by and between the Company and Antecip Bioventures II LLC (Incorporated by reference, Exhibit 10.3 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
10.6*	License Agreement, dated June 6, 2012, by and between the Company and Antecip Bioventures II LLC, as modified by the First Amendment to License Agreement, dated August 21, 2015, by and between the Company and Antecip Bioventures II LLC (Incorporated by reference, Exhibit 10.4 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
10.7+	Consulting Agreement, dated April 13, 2012, by and between the Company and Mark Coleman, M.D., as modified by the First Amendment to Consulting Agreement, dated June 2, 2014, by and between the Company and Mark Coleman, M.D (Incorporated by reference, Exhibit 10.5 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
10.8	Loan and Security Agreement, dated as of November 9, 2016, by and between Axsome Therapeutics, Inc., and Silicon Valley Bank (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K filed November 10, 2016.)

10.9+	John Golubieski Offer Letter, dated July 5, 2017 (Incoporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed August 9, 2017.)
10.10	Form of Purchase Agreement, dated as of November 30, 2017 among Axsome Therapeutics, Inc. and the purchasers thereunder (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K filed December 4, 2017.)
21.1	Subsidiaries of the Company (Incorporated by reference, Exhibit 21.1 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015.)
23.1	Consent of Ernst & Young LLP.
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a)/15d-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a)/15d-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification of Principal Executive Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (furnished herewith).
32.2	Certification of Principal Financial Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (furnished herewith).
101	Interactive data files pursuant to Rule 405 of Regulation S-T: (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations, (iii) Consolidated Statements of Cash Flows, and (iv) the Notes to Consolidated Financial Statements.

+ Indicates management contract or compensatory plan.

* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

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 7th day of March 2018.

AXSOME THERAPEUTICS, INC.

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

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this report has been signed by the following persons on behalf of the registrant and in the capacities and on the dates indicated:

Signature	Title	Date
/s/ Herriot Tabuteau, M.D. Herriot Tabuteau, M.D.	Chief Executive Officer and Chairman of the Board (Principal Executive Officer)	March 7, 2018
/s/ John Golubieski John Golubieski	Chief Financial Officer (Principal Financial and Accounting Officer)	March 7, 2018
/s/ Roger Jeffs, Ph.D. Roger Jeffs, Ph.D.	Director	March 7, 2018
/s/ Mark Coleman, M.D. Mark Coleman, M.D.	Director	March 7, 2018
/s/ Mark Saad Mark Saad	Director	March 7, 2018
/s/ Myrtle Potter Myrtle Potter	Director	March 7, 2018

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statements:

- Registration Statement (Form S-8 No. 333-217002) pertaining to the Axsome Therapeutics, Inc. 2015 Omnibus Incentive Compensation Plan,
- Registration Statement (Form S-8 No. 333-208579) pertaining to the Axsome Therapeutics, Inc. 2015 Omnibus Incentive Compensation Plan, and
- Registration Statement (Form S-3 No. 333-214859) of Axsome Therapeutics, Inc. and in the related Prospectus;

of our report dated March 7, 2018, 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, 2017.

/s/ Ernst & Young LLP

New York, NY
March 7, 2018

Exhibit 31.1

CERTIFICATION OF PERIODIC REPORT
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Herriot Tabuteau, certify that:

1. I have reviewed this annual report on Form 10-K of Axsome Therapeutics, Inc.;

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

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

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

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

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Date: March 7, 2018

/s/ Herriot Tabuteau
Herriot Tabuteau
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF PERIODIC REPORT PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, John Golubieski, 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 7, 2018

/s/ John Golubieski
John Golubieski
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

STATEMENT OF PRINCIPAL EXECUTIVE OFFICER OF
AXSOME THERAPEUTICS, INC.
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of Axsome Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2017 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 7, 2018

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

Exhibit 32.2

STATEMENT OF PRINCIPAL FINANCIAL OFFICER OF
AXSOME THERAPEUTICS, INC.
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of Axsome Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2017 as filed with the Securities and Exchange Commission (the "Report"), I, John Golubieski, 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 7, 2018

/s/ John Golubieski
John Golubieski
Chief Financial Officer
(Principal Financial and Accounting Officer)