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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-214859

The information contained in this preliminary prospectus supplement and the accompanying prospectus is not complete and may be changed. A registration statement relating to the securities has been declared effective by the Securities and Exchange Commission. This preliminary prospectus supplement and the accompanying prospectus do not constitute an offer to sell these securities and we are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MARCH 20, 2017

PRELIMINARY PROSPECTUS SUPPLEMENT
(To Prospectus dated December 16, 2016)



Common Stock

Axsome Therapeutics, Inc. is offering _____ shares of common stock.

Our common stock is listed on The NASDAQ Global Market under the symbol "AXSM." The last reported sale price of our common stock on The NASDAQ Global Market on March 17, 2017 was \$4.55 per share.

As of March 13, 2017, the aggregate market value of our outstanding common stock held by non-affiliates was approximately \$58,717,864, based on 19,196,316 shares of outstanding common stock, of which approximately 8,011,961 shares were held by affiliates, and a price of \$5.25 per share, which was the last reported sale price of our common stock on March 13, 2017. As of the date of this prospectus supplement, we have not offered any securities pursuant to General Instruction I.B.6. of Form S-3 during the prior 12 calendar month period that ends on, and includes, the date of this prospectus supplement.

We are an emerging growth company as that term is used in the Jumpstart Our Business Startups Act of 2012 and, as such, have elected to comply with certain reduced public company reporting requirements.

Investing in our common stock involves a high degree of risk. See "Risk Factors" beginning on page S-5 and in the documents incorporated by reference in this prospectus supplement.

	<i>Per Share</i>	<i>Total</i>
Public offering price	\$	\$
Underwriting discounts and commissions(1)	\$	\$
Offering proceeds to us, before expenses	\$	\$

(1) We refer you to the section entitled "Underwriting" beginning on page S-21 of this prospectus supplement for additional information regarding total underwriter compensation.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

We have granted the underwriter the right to purchase up to _____ additional shares of common stock. The underwriter can exercise this right at any time within 30 days after the offering. The underwriter expects to deliver the shares of common stock to investors on or about _____, 2017.

Sole Book-running Manager

Ladenburg Thalmann

_____, 2017

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Neither we nor the underwriter have authorized anyone to provide any information or to make any representations other than those contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus we have authorized for use in connection with this offering. We and the underwriter take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus together constitute an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering is current only as of its date. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference herein and therein, and any free writing prospectus that we have authorized for use in connection with this offering when making your investment decision. You should also read and consider the information in the documents we have referred you to in the sections of this prospectus supplement and the accompanying prospectus entitled "Where You Can Find More Information" and "Information Incorporated by Reference."

ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus form part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, utilizing a "shelf" registration process. This document contains two parts. The first part consists of this prospectus supplement, which provides you with specific information about this offering. The second part, the accompanying prospectus, provides more general information, some of which may not apply to this offering. Generally, when we refer only to the "prospectus," we are referring to both parts combined. This prospectus supplement may add, update or change information contained in the accompanying prospectus. To the extent that any statement we make in this prospectus supplement is inconsistent with statements made in the accompanying prospectus or any documents incorporated by reference herein or therein, the statements made in this prospectus supplement will be deemed to modify or supersede those made in the accompanying prospectus and such documents incorporated by reference herein and therein. You should read this prospectus supplement and the accompanying prospectus, including the information incorporated by reference herein and therein, and any related free writing prospectus that we have authorized for use in connection with this offering.

You should rely only on the information that we have included or incorporated by reference in this prospectus supplement, the accompanying prospectus, and any related free writing prospectus that we may authorize to be provided to you. We have not authorized any dealer, salesman, or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus supplement, the accompanying prospectus, or any related free writing prospectus that we may authorize to be provided to you. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus supplement, the accompanying prospectus, or any related free writing prospectus.

This prospectus supplement, the accompanying prospectus, and any related free writing prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus supplement, the accompanying prospectus, or any related free writing prospectus constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction.

You should not assume that the information contained in this prospectus supplement, the accompanying prospectus, or any related free writing prospectus is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference herein or therein is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus supplement, accompanying prospectus, or any related free writing prospectus is delivered, or securities are sold, on a later date.

This prospectus supplement contains or incorporates by reference summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been or will be filed or have been or will be incorporated by reference as exhibits to the registration statement of which this prospectus supplement forms a part, and you may obtain copies of those documents as described in this prospectus supplement under the heading "Where You Can Find More Information."

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Certain matters discussed in this prospectus supplement and the accompanying prospectus, including matters discussed under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations," incorporated by reference herein, 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. We may, in some cases, use terms such as "predicts," "believes," "potential," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," or other words that convey uncertainty of future events or outcomes to identify these 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 headings "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this prospectus supplement and the documents incorporated by reference herein, as well as other factors which may be identified from time to time in our other filings with 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.

In particular, our statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation and completion of the trials; the timing of and our ability to obtain and maintain FDA or other regulatory authority approval of, or other action with respect to, our product candidates; our ability to obtain additional capital necessary to fund our operations; our ability to generate revenues in the future; our ability to successfully defend our intellectual property or obtain the necessary licenses at a cost acceptable to us, if at all; the successful implementation of our research and development programs; the enforceability of our license agreements; the acceptance by the market of our product candidates, if approved; and other factors, including general economic conditions and regulatory developments, not within our control and discussed under the heading "Risk Factors," including those risk factors that are incorporated by reference in this prospectus supplement and the accompanying prospectus.

The forward-looking statements contained in this prospectus supplement and the accompanying prospectus reflect our views and assumptions only as of the date of this prospectus supplement. 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.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights information contained in other parts of this prospectus supplement. Because it is only a summary, it does not contain all of the information that you should consider before investing in shares of our common stock and it is qualified in its entirety by, and should be read in conjunction with, the more detailed information appearing elsewhere in this prospectus supplement, the accompanying prospectus, any applicable free writing prospectus and the documents incorporated by reference herein and therein. You should read all such documents carefully, especially the risk factors and our consolidated financial statements and the related notes included or incorporated by reference herein or therein, before deciding to buy shares of our common stock. Unless the context requires otherwise, references in this prospectus to "Axsome," "we," "us," and "our" refer to Axsome Therapeutics, Inc.

Company 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 two late-stage candidates, AXS-05 and AXS-02, which we are developing for multiple indications. We have initiated a Phase 3 trial with AXS-05 in treatment resistant depression, or TRD, which we refer to as the STRIDE-1 study, and plan to initiate a Phase 2/3 trial in agitation in patients with Alzheimer's disease, or AD. We have also initiated a Phase 3 trial with AXS-02 in complex regional pain syndrome, or CRPS, which we refer to as the CREATE-1 study, and 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 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.

Our first product candidate, AXS-05, is an innovative fixed-dose combination of dextromethorphan, or DM, and bupropion. We are developing AXS-05 initially for the treatment of the following two conditions: TRD and agitation in patients with AD. 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.

Our second product candidate, 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 three conditions: CRPS; knee OA associated with BMLs; and chronic low back pain, or CLBP, associated with type 1 or mixed type 1 and type 2 Modic changes, or 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-02 has been granted Orphan Drug Designation by the FDA and Orphan Medicinal Product Designation by the European Medicines Agency, or EMA, for the treatment of CRPS.

We are currently evaluating preclinical product candidates, including AXS-06, which we intend to develop for CNS disorders, including chronic pain.

Our current product candidate pipeline is summarized in the graphic below:



Abbreviations: BUP = Bupropion; DM = Dextromethorphan; CRPS = Complex Regional Pain Syndrome; OA = Osteoarthritis; BML = Bone Marrow Lesions; SPA = Special Protocol Assessment; CLBP = Chronic Low Back Pain; MC = Modic Changes.

Recent Developments

On January 3, 2017, we issued a press release announcing that we have received, from the FDA, clearance of our Investigational New Drug Application, or IND, for AXS-05 for the treatment of agitation in patients with AD. Such clearance permits us to proceed with our planned Phase 2/3 clinical trial of AXS-05 in this indication. We anticipate commencing this trial in the second quarter of 2017.

On February 3, 2017, we received, from the FDA, clearance of our IND for AXS-02 for the treatment of CLBP associated with MCs. Such clearance permits us to proceed with our planned Phase 3 clinical trial of AXS-02 in this indication. The start of this trial is contingent upon the availability of resources.

On February 14, 2017, we issued a press release announcing that we have received, from the FDA, Fast Track designation for AXS-05 for the treatment of TRD.

On March 7, 2017, we issued a press release announcing that an interim analysis will now be performed by an independent data monitoring committee on the first approximately 60 subjects enrolled in the COAST-1 study, our Phase 3 trial of AXS-02 in knee OA associated with BMLs, to assess the assumptions used to determine the sample size of the study. Screening of subjects in this trial will be paused pending results of the interim analysis, and will resume after readouts from our other ongoing Phase 3 trials in CRPS and TRD.

Corporate Information

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

Information concerning our business and our prospects is included in the documents that we file with the SEC as a reporting company under the Securities Exchange Act of 1934, which are accessible at www.sec.gov, and on our website at www.axsome.com. The public can also obtain copies of these filings by visiting the SEC's Public Reference Room at 100 F Street NE, Washington D.C. 20549, or by calling the SEC at 1-800-SEC-0330. The information contained on, or that can be accessed through, our website is not a part of this prospectus supplement. Investors should not rely on any such information in deciding whether to purchase our common stock. We have included our website address in this prospectus supplement solely as an inactive textual reference.

Implications of Being an Emerging Growth Company

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. An emerging growth company may take advantage of relief from certain reporting requirements and other burdens that are otherwise generally applicable to public companies. These provisions include:

- only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- exemption from the auditor attestation requirement on the effectiveness of our internal controls over financial reporting;
- reduced disclosure about our executive compensation arrangements; and
- no requirements for non-binding advisory votes on executive compensation or golden parachute arrangements.

We may take advantage of these provisions for up to five years from the date of our initial public offering in November 2015 or such earlier time that we no longer qualify as an emerging growth company. We would cease to be an emerging growth company if we have more than \$1.0 billion in annual revenue, have more than \$700 million in market value of our capital stock held by non-affiliates or issue more than \$1.0 billion of non-convertible debt over a three-year period. We may choose to take advantage of some but not all of these reduced reporting requirements and other burdens. We have taken advantage of some reduced reporting burdens in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein. Accordingly, the information that we provide stockholders may be different than you might obtain from other public companies in which you hold equity interests.

THE OFFERING

Common stock offered by us	shares	
Total common stock to be outstanding after this offering	shares, or	shares if the underwriter exercises its option to purchase additional shares in full.
Option to purchase additional shares	The underwriter has an option for a period of 30 days to purchase up to additional shares of our common stock.	
Use of proceeds	We intend to use the net proceeds of this offering to fund the ongoing clinical development of our late-stage product candidates, AXS-05 and AXS-02, and other general corporate purposes. See "Use of Proceeds."	
Risk factors	You should read the "Risk Factors" section of this prospectus supplement beginning on page S-5 as well as those risk factors that are incorporated by reference in this prospectus supplement and the accompanying prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.	
NASDAQ Global Market symbol	AXSM	

The number of shares of our common stock that will be outstanding immediately after this offering is based on 19,158,417 shares of our common stock outstanding as of December 31, 2016. This calculation excludes:

- 1,772,050 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2016, at a weighted average exercise price of \$5.74 per share;
- 337,696 shares of common stock issuable upon the exercise of outstanding warrants as of December 31, 2016, consisting of 230,409 warrants with an exercise price of \$1.30 per share, 42,059 warrants with an exercise price of \$5.94 per share, and 65,228 warrants with an exercise price of \$7.41 per share; and
- 2,718,725 shares of common stock as of December 31, 2016 available for future grant under our 2015 Omnibus Incentive Compensation Plan, or the 2015 Plan.

Unless otherwise indicated herein, all information in this prospectus supplement, including the number of shares that will be outstanding after this offering reflects and assumes the following:

- no exercise of the underwriter's option to purchase additional shares; and
- no exercise of outstanding options or warrants after December 31, 2016.

RISK FACTORS

An investment in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should carefully consider the risks described below and those discussed under the section captioned "Risk Factors" contained in our Annual Report on Form 10-K for the year ended December 31, 2016, which is incorporated by reference in this prospectus supplement and the accompanying prospectus, together with other information in this prospectus supplement, the accompanying prospectus, the information and documents incorporated by reference herein and therein, and in any free writing prospectus that we have authorized for use in connection with this offering. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment.

Risks Related to This Offering

We have incurred significant losses since our inception and anticipate that we will incur substantial and increasing losses for the foreseeable future. We may never achieve or maintain profitability, which would depress the market price of our common stock, and could cause you to lose all or a part of your investment.

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-05 and AXS-02, with the goal of achieving regulatory approval. Since inception, we have incurred significant operating losses. Our net losses were \$27.2 million and \$12.2 million for the years ended December 31, 2016 and 2015, respectively. As of December 31, 2016, we had an accumulated deficit of \$47.6 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 AXS-05, AXS-02, and our other current and future product candidates. In addition, we expect to incur significant sales, marketing, and manufacturing expenses related to the commercialization of AXS-05, AXS-02, and our other 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 continue to progress the development of AXS-05 and AXS-02.

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.

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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.

The price of our common stock may be volatile and fluctuate substantially, and you may not be able to resell your shares at or above the public offering price.

The public offering price for our shares will be determined by negotiations between us and the underwriter and may not be indicative of prices that actually prevail in the trading market either before or after this offering. Since our initial public offering in November 2015, the trading price of our common stock has been, and we expect it to continue 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 ongoing or planned clinical trials for AXS-05 and AXS-02;
- any delay or refusal on the part of the FDA in approving a new drug application, or NDA, for AXS-05, AXS-02, or any other of our current and future product candidates;
- the commercial success of AXS-05, AXS-02, and any other of our current and future product candidates, if approved by the FDA;
- results of clinical trials of AXS-05, AXS-02, and any other of our current and future product candidates or those of our competitors;
- the level of expenses related to any of our product candidates or clinical development programs;
- 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;
- developments concerning our sources of manufacturing supply, warehousing, and inventory control or service providers for our clinical trials;
- 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;

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- announcements and expectations of additional financing efforts, including the issuance by us of debt, equity, or convertible securities;
- sales of our common stock, including sales by our directors and officers or significant stockholders;
- actual or anticipated changes in the financial results, development timelines, or 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 and in Part I, Item 1A "Risk Factors" of our Annual Report on Form 10-K filed with the SEC on March 7, 2017.

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.

We will need to obtain additional financing to fund our operations and, if we are unable to obtain such financing, we may be unable to complete the development and commercialization of our product candidates.

Conducting clinical trials, pursuing regulatory approvals, establishing outsourced manufacturing relationships, and successfully manufacturing and commercializing our product candidates, including AXS-05 and AXS-02, 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 AXS-05, AXS-02, and our other 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, including AXS-06; and
- in-license other product candidates.

We believe that with the net proceeds from this offering, together with our existing cash, we will have sufficient funds to meet our anticipated operating cash requirements through . 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 either AXS-05 or AXS-02 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 AXS-05 and AXS-02. Our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress and costs related to our Phase 3 development of AXS-05 and AXS-02;

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- 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 AXS-05 and AXS-02, and any costs associated with such delays;
- the costs of establishing a commercial organization to sell, market, and distribute AXS-05 and AXS-02;
- the rate of progress and costs of our efforts to prepare for the submission of a 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 AXS-05 and AXS-02 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 AXS-05, AXS-02, and any other 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.

Management will have broad discretion as to the use of the proceeds from this offering, and we may not use the proceeds effectively.

Our management will have broad discretion with respect to the use of proceeds of this offering, including for any of the purposes described in the section of this prospectus supplement entitled "Use of Proceeds." You will be relying on the judgment of our management regarding the application of the proceeds of this offering. The results and effectiveness of the use of proceeds are uncertain, and we could spend the proceeds in ways that you do not agree with or that do not improve our results of operations or enhance the value of our common stock. Our failure to apply these funds effectively could have a material adverse effect on our business, delay the development of our product candidates, and cause the price of our common stock to decline.

You will experience immediate and substantial dilution in the net tangible book value per share of the common stock you purchase.

Since the public offering price for our common stock in this offering is substantially higher than the net tangible book value per share of our common stock outstanding prior to this offering, you will

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suffer immediate and substantial dilution in the net tangible book value of the common stock you purchase in this offering. Based on the public offering price of \$ per share, if you purchase shares in this offering, you will suffer immediate dilution of \$ per share in the net tangible book value of the common stock. If the underwriter exercises its option to purchase additional shares, you will experience additional dilution. See the section entitled "Dilution" below for a more detailed discussion of the dilution you will incur if you purchase shares in this offering.

We have never declared or paid dividends on our capital stock and we do not anticipate paying dividends in the foreseeable future.

Our business requires significant funding, and we currently invest available funds and earnings in product development. Therefore, we do not anticipate paying any cash dividends on our common stock in the foreseeable future. We currently plan to invest all available funds and future earnings in the development and growth of our business. As a result, capital appreciation, if any, of our common stock will be your sole source of potential gain for the foreseeable future.

A significant portion of our total outstanding shares is restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to decline significantly.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares of common stock intend to sell shares, could reduce the market price of our common stock. After this offering, we will have shares of common stock outstanding based on the 19,158,417 shares outstanding as of December 31, 2016 and the issuance and sale of shares of our common stock in this offering. Of these shares, 8,037,745 shares are subject to a contractual lock-up with the underwriter for this offering for a period of 90 days following this offering. These shares can be sold, subject to any applicable volume limitations under federal securities laws, after the earlier of the expiration of, or release from, the 90-day lock-up period. The balance of our outstanding shares of common stock may be freely sold in the public market at any time, subject to volume limitations applicable to affiliates.

In addition, as of December 31, 2016, there were 1,772,050 shares subject to outstanding options under our 2015 Plan, all of which shares we have registered under the Securities Act of 1933, as amended, which we refer to as the Securities Act, on a registration statement on Form S-8. These shares, once vested and issued upon exercise, will be able to be freely sold in the public market, subject to volume limits applicable to affiliates and the lock-up agreements described above, to the extent applicable. Furthermore, as of December 31, 2016, there were 337,696 shares subject to outstanding warrants. The shares underlying these warrants will become eligible for sale in the public market to the extent such warrants are exercised and to the extent permitted by Rule 144 under the Securities Act.

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, 2016, we had U.S. net operating loss carryforwards of approximately \$37 million. Our net operating loss carryforwards will begin expiring in 2033 if we have not used them prior to that time. 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 Internal Revenue Code Sections 382 and 383, respectively, if we have a cumulative change in ownership of more than 50% within a three-year period. The completion of this offering, together with 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

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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.

USE OF PROCEEDS

We estimate that the net proceeds from the sale of _____ shares of our common stock that we are offering will be approximately \$ _____ million, based on the public offering price of \$ _____ per share, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriter exercises its option to purchase additional shares in full, we estimate that we will receive net proceeds of approximately \$ _____ million after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

We currently intend to use the net proceeds from this offering to fund our ongoing clinical programs, including our late-stage clinical trials with AXS-05 and AXS-02, and for working capital and general corporate purposes.

As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses of the net proceeds to be received upon the completion of this offering. The amounts and timing of our actual expenditures will depend on numerous factors, including the progress of our development efforts, the status of and results from clinical trials, any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. Accordingly, our management will have broad discretion in the application of the net proceeds from this offering and investors will be relying on the judgment of our management regarding the application of the net proceeds from this offering.

We anticipate that the net proceeds from this offering, together with our existing cash, will be sufficient to enable us to fund our anticipated operating requirements through _____. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. See the "Risk Factors" section of this prospectus supplement and the documents incorporated by reference for a discussion of the risks affecting our business that could have an adverse effect on our available capital resources.

Until we use the net proceeds of this offering for the above purposes, we intend to invest the funds in short-term, investment-grade, interest-bearing instruments and U.S. government securities. We cannot predict whether these investments will yield a favorable return.

PRICE RANGE OF COMMON STOCK

Our common stock was listed on The NASDAQ Capital Market under the symbol "AXSM" between November 19, 2015 and March 2, 2017. Effective as of March 3, 2017, our common stock has been listed on The NASDAQ Global Market under the same symbol. Prior to our initial public offering, there was no public market for our common stock. The following table sets forth for the periods indicated the high and low sale prices per share of our common stock:

	<u>High</u>	<u>Low</u>
Year Ended December 31, 2017		
First Quarter (through March 17, 2017)	\$ 7.10	\$ 4.00
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
Year Ended December 31, 2015		
Fourth Quarter (from November 19, 2015)	\$ 9.70	\$ 8.00

On March 17, 2017, the last sale price of our common stock, as reported on The NASDAQ Global Market, was \$4.55.

DIVIDEND POLICY

We have not declared or paid any cash dividends on our capital stock since our inception. We currently anticipate that we will retain future earnings, if any, for the development, operation, and expansion of our business and do not anticipate declaring or paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be at the discretion of our board of directors and will depend upon a number of factors, including our results of operations, financial condition, future prospects, contractual restrictions, restrictions imposed by applicable law, and other factors our board of directors deems 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. As a result, we anticipate that only appreciation of the price of our common stock, if any, will provide a return to investors in this offering for at least the foreseeable future.

CAPITALIZATION

The following table describes our capitalization as of December 31, 2016:

- on an actual basis; and
- on an as adjusted basis to reflect our issuance and sale of _____ shares of our common stock in this offering at the public offering price of \$ _____ per share, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this data in conjunction with our historical financial statements and the related notes incorporated by reference in this prospectus supplement and the section entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations" contained in our most recent Annual Report filed on Form 10-K and other information on file with the SEC that is incorporated by reference in this prospectus supplement and the accompanying prospectus.

	As of December 31, 2016	
	Actual	As Adjusted ⁽¹⁾
Cash	\$ 36,618,497	
Preferred stock, \$0.0001 par value per share; 10,000,000 shares authorized, no shares issued or outstanding, actual or as adjusted	—	—
Common stock, \$0.0001 par value per share, 150,000,000 shares authorized, 19,158,417 shares issued and outstanding, actual; 150,000,000 shares authorized, _____ shares issued and outstanding, as adjusted	1,916	
Additional paid-in capital	69,210,986	
Accumulated deficit	(47,641,451)	
Total stockholders' equity	21,571,451	
Total capitalization	\$ 21,571,451	

- (1) The as adjusted balance sheet data reflects the sale of _____ shares of common stock offered by us in this offering at the public offering price of \$ _____ per share, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The preceding table excludes:

- 1,772,050 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2016, at a weighted average exercise price of \$5.74 per share;
- 337,696 shares of common stock issuable upon the exercise of outstanding warrants as of December 31, 2016, consisting of 230,409 warrants with an exercise price of \$1.30 per share, 42,059 warrants with an exercise price of \$5.94 per share, and 65,228 warrants with an exercise price of \$7.41 per share; and
- 2,718,725 shares of common stock as of December 31, 2016 available for future grant under our 2015 Plan.

DILUTION

If you invest in our common stock, your interest will be diluted immediately to the extent of the difference between the public offering price per share you will pay in this offering and the as adjusted net tangible book value per share of our common stock after this offering. Net tangible book value per share represents our total tangible assets less total liabilities, divided by the number of shares of our common stock outstanding.

As of December 31, 2016, our net tangible book value was \$21,571,451, or \$1.13 per share of common stock. After giving effect to our issuance and sale of _____ shares of common stock in this offering at the public offering price of \$ _____ per share, after deducting the estimated underwriting discounts and commissions and the estimated offering expenses payable by us, the as adjusted net tangible book value as of December 31, 2016 would have been \$ _____, or \$ _____ per share. This represents an immediate increase in as adjusted net tangible book value to existing stockholders of \$ _____ per share and an immediate dilution to new investors purchasing common stock in this offering of \$ _____ per share.

The following table illustrates this per share dilution to the new investors purchasing shares of common stock in this offering:

Public offering price per share	\$
Net tangible book value per share at December 31, 2016	1.13
Increase in net tangible book value per share attributable to new investors purchasing shares in this offering	_____
As adjusted net tangible book value per share after this offering	_____
Dilution per share to new investors in this offering	\$ _____

If the underwriter exercises its option to purchase additional shares in full, or if any additional shares are issued upon exercise of outstanding options or warrants, you will experience further dilution.

The foregoing table and calculations are based on 19,158,417 shares of our common stock outstanding as of December 31, 2016, and excludes 337,696 shares of common stock issuable upon the exercise of outstanding warrants as of December 31, 2016, consisting of 230,409 warrants with an exercise price of \$1.30 per share, 42,059 warrants with an exercise price of \$5.94 per share, and 65,228 warrants with an exercise price of \$7.41 per share, 1,772,050 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2016, at a weighted average exercise price of \$5.74 per share, and 2,718,725 shares of common stock that remain available under our 2015 Plan for future grants.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following is a general discussion of the material U.S. federal income tax consequences of the acquisition, ownership and disposition of our common stock by "Non-U.S. Holders" (as defined below). This discussion is a summary for general information purposes only and does not consider all aspects of U.S. federal income taxation that may be relevant to particular Non-U.S. Holders in light of their individual circumstances or to certain types of Non-U.S. Holders subject to special tax rules under the Internal Revenue Code of 1986, as amended, or the Code, including partnerships or other pass-through entities for U.S. federal income tax purposes, banks, financial institutions or other financial services entities, broker-dealers, insurance companies, tax-exempt organizations, regulated investment companies, real estate investment trusts, controlled foreign corporations, passive foreign investment companies, corporations that accumulate earnings to avoid U.S. federal income tax, persons who use or are required to use mark-to-market accounting, persons that hold our shares as part of a "straddle," a "hedge" or a "conversion transaction," persons for whom our stock constitutes "qualified small business stock" within the meaning of Section 1202 of the Code, certain former citizens or permanent residents of the United States, or investors in pass-through entities. In addition, this summary does not address the effects of any applicable gift or estate tax, and this summary does not address the potential application of the alternative minimum tax, Medicare contribution tax, or any tax considerations that may apply to Non-U.S. Holders of our common stock under state, local, or non-U.S. tax laws or any other U.S. federal tax laws.

This summary is based on the Code, and applicable Treasury Regulations, rulings, administrative pronouncements, and decisions as of the date of this registration statement, all of which are subject to change or differing interpretations at any time with possible retroactive effect. We have not sought, and will not seek, any ruling from the Internal Revenue Service, or the IRS, with respect to the tax consequences discussed herein, and there can be no assurance that the IRS will not take a position contrary to the tax consequences discussed below or that any position taken by the IRS would not be sustained. This discussion assumes that a Non-U.S. Holder will hold our common stock as a "capital asset" within the meaning of Section 1221 of the Code (generally, property held for investment).

The following discussion is for general information only and is not tax advice for any Non-U.S. Holder under its particular circumstances. Persons considering the purchase of our common stock pursuant to this offering should consult their tax advisors concerning the U.S. federal income, estate, and gift tax consequences of acquiring, owning, and disposing of our common stock in light of their particular situations as well as any consequences arising under the laws of any other taxing jurisdiction, including any state, local, and non-U.S. tax consequences and the possible application of tax treaties that might change the general provisions discussed below.

For purposes of this discussion, the term "Non-U.S. Holder" means a beneficial owner of our shares that is not a partnership (or entity or arrangement treated as a partnership for U.S. federal income tax purposes) or an entity that is treated as a disregarded entity for U.S. federal income tax purposes and is not:

- an individual who is a citizen or resident of the United States;
- a corporation (or other entity treated as a corporation for U.S. federal income tax purposes) created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust if (1) a U.S. court can exercise primary supervision over the trust's administration and one or more U.S. persons have the authority to control all of the trust's substantial decisions or (2) the trust has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a U.S. person for U.S. federal income tax purposes.

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If a partnership (or entity or arrangement treated as a partnership for U.S. federal income tax purposes) or an entity that is treated as a disregarded entity for U.S. federal income tax purposes (regardless of its place of organization or formation) is a beneficial owner of our common stock, the tax treatment of such partnership, and a partner in the partnership, or the owner of the disregarded entity generally will depend upon the status of the partner or the owner of the disregarded entity and the activities of the partnership or the disregarded entity. If you are a partnership holding our common stock, or a partner of such partnership, or the owner of a disregarded entity holding our common stock, you should consult your tax advisor regarding the tax consequences of the purchase, ownership, and disposition of our common stock.

There are certain tax reform proposals currently being considered in connection with the new Republican administration. While it is uncertain whether any such proposals would be enacted into law, and it is impossible to predict whether this will be the case, if any such proposals were to become law, they could materially change the U.S. federal income tax consequences described below.

PROSPECTIVE INVESTORS SHOULD CONSULT THEIR TAX ADVISORS REGARDING THE PARTICULAR U.S. FEDERAL INCOME TAX CONSEQUENCES TO THEM OF ACQUIRING, OWNING AND DISPOSING OF OUR COMMON STOCK, AS WELL AS ANY TAX CONSEQUENCES ARISING UNDER ANY STATE, LOCAL OR FOREIGN TAX LAWS AND ANY OTHER U.S. FEDERAL TAX LAWS.

Distributions on Our Common Stock

In general, subject to the discussion below under "Information Reporting and Backup Withholding" and "Foreign Accounts," distributions, if any, paid to a Non-U.S. Holder (to the extent paid out of our current or accumulated earnings and profits, as determined under U.S. federal income tax principles) will constitute dividends and be subject to U.S. withholding tax at a rate equal to 30% of the gross amount of the dividend, or a lower rate prescribed by an applicable income tax treaty, unless the dividends are effectively connected with a trade or business carried on by the Non-U.S. Holder within the United States. Any distribution not constituting a dividend (because such distribution exceeds our current and accumulated earnings and profits) will be treated first as reducing the Non-U.S. Holder's basis in its shares of common stock, but not below zero, and to the extent it exceeds the Non-U.S. Holder's basis, as capital gain and will be treated as described below under "Gain on Sale, Exchange or Other Disposition of Our Common Stock."

A Non-U.S. Holder who claims the benefit of an applicable income tax treaty generally will be required to satisfy certain certification and other requirements prior to the distribution date. Non-U.S. Holders must generally provide the withholding agent with a properly executed IRS Form W-8BEN, Form W-8BEN-E or other appropriate form claiming an exemption from or reduction in withholding under an applicable income tax treaty. This certification must be updated periodically. If a Non-U.S. Holder holds our common stock through a financial institution or other agent acting on the Non-U.S. Holder's behalf, the Non-U.S. Holder will be required to provide appropriate documentation to the agent, who then will be required to provide certification to us or our paying agent, either directly or through other intermediaries. If tax is withheld in an amount in excess of the amount applicable under an income tax treaty, a refund of the excess amount may generally be obtained by timely filing an appropriate claim for refund with the IRS. Non-U.S. Holders should consult their tax advisors regarding their entitlement to benefits under an applicable income tax treaty.

Dividends that are effectively connected with a Non-U.S. Holder's conduct of a U.S. trade or business (and, if required by an applicable income tax treaty, attributable to a U.S. permanent establishment or fixed base of the Non-U.S. Holder) generally will not be subject to U.S. withholding tax if the Non-U.S. Holder provides the withholding agent with the required forms, including IRS Form W-8ECI, but instead generally will be subject to U.S. federal income tax on a net income basis at

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the regular graduated rates in the same manner as if the Non-U.S. Holder were a resident of the United States. A corporate Non-U.S. Holder that receives effectively connected dividends may also be subject to an additional branch profits tax at a rate of 30% (or a lower rate prescribed by an applicable income tax treaty) of its effectively connected earnings and profits for the taxable year, as adjusted for certain items.

Gain on Sale, Exchange or Other Disposition of Our Common Stock

In general, a Non-U.S. holder will not be subject to any U.S. federal income tax or withholding tax on any gain realized upon such holder's sale, exchange or other disposition of shares of our common stock unless:

- (i) the gain is effectively connected with a trade or business carried on by the Non-U.S. Holder within the United States (and, if required by an applicable income tax treaty, attributable to a U.S. permanent establishment or fixed base of the Non-U.S. Holder);
- (ii) the Non-U.S. Holder is an individual who is present in the United States for 183 days or more in the taxable year of disposition and certain other conditions are met; or
- (iii) we are or have been a "United States real property holding corporation" for U.S. federal income tax purposes at any time during the shorter of the five-year period ending on the date of disposition or the period that the Non-U.S. Holder held the common stock, and, in the case where shares of our common stock are regularly traded on an established securities market, the Non-U.S. Holder owns, or is treated as owning, more than five percent of our common stock at any time during the foregoing period.

Net gain realized by a Non-U.S. Holder described in clause (i) above generally will be subject to U.S. federal income tax in the same manner as if the Non-U.S. Holder were a U.S. person. Any gains of a corporate Non-U.S. Holder described in clause (i) above may also be subject to an additional branch profits tax at a 30% rate, or such lower rate as may be specified by an applicable income tax treaty.

Gain realized by an individual Non-U.S. Holder described in clause (ii) above will be subject to a flat 30% (or such lower rate specified by an applicable income tax treaty) tax, which gain may be offset by certain U.S. source capital losses, even though the individual is not considered a resident of the United States, provided that the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

For purposes of clause (iii) above, a corporation is a "United States real property holding corporation" if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. We believe that we are not, and we do not anticipate that we will become, a United States real property holding corporation. However, because the determination of whether we are a United States real property holding corporation depends on the fair market value of our U.S. real property interests relative to the fair market value of our other business assets, there can be no assurance that we will not become a United States real property holding corporation in the future. If we become a United States real property holding corporation, as long as our common stock is regularly traded on an established securities market, our common stock will be treated as a U.S. real property interest only with respect to a Non-U.S. Holder that actually or constructively held more than 5% of our common stock at any time during the shorter of the two periods described in clause (iii), above. If gain on the sale or other taxable disposition of our common stock were subject to taxation under clause (iii) above, the Non-U.S. Holder would be subject to regular U.S. federal income tax with respect to such gain in generally the same manner as a U.S. person.

Information Reporting and Backup Withholding

Generally, we must report annually to the IRS and to each Non-U.S. Holder the amount of dividends paid, the name and address of the recipient, and the amount, if any, of tax withheld. These information reporting requirements apply even if withholding was not required because the dividends were effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States or withholding was reduced by an applicable income tax treaty. Under applicable income tax treaties or other agreements, the IRS may make its reports available to the tax authorities in the Non-U.S. Holder's country of residence.

Dividends paid to a Non-U.S. Holder that is not an exempt recipient generally will be subject to backup withholding, currently at a rate of 28%, unless the Non-U.S. Holder certifies to the withholding agent as to its foreign status, which certification may generally be made on IRS Form W-8BEN, Form W-8BEN-E or other appropriate version of IRS Form W-8. Notwithstanding the foregoing, backup withholding may apply if either we or our paying agent has actual knowledge, or reason to know, that the holder is a U.S. person that is not an exempt recipient.

Proceeds from the sale or other disposition of common stock by a Non-U.S. Holder effected by or through a U.S. office of a broker will generally be subject to information reporting and backup withholding, currently at a rate of 28%, unless the Non-U.S. Holder certifies to the withholding agent under penalties of perjury as to, among other things, its name, address and status as a Non-U.S. Holder or otherwise establishes an exemption. Subject to the discussion below under "Foreign Accounts," payment of disposition proceeds effected outside the U.S. by or through a non-U.S. office of a non-U.S. broker generally will not be subject to information reporting or backup withholding if the payment is not received in the United States. Information reporting, but generally not backup withholding (provided the broker does not have actual knowledge or reason to know that the holder is a U.S. person that is not an exempt recipient), will apply to such a payment if the broker has certain connections with the United States unless the broker has documentary evidence in its records that the beneficial owner thereof is a Non-U.S. Holder and specified conditions are met or an exemption is otherwise established.

Backup withholding is not an additional tax. Any amount withheld under the backup withholding rules from a payment to a Non-U.S. Holder that results in an overpayment of taxes generally will be refunded, or credited against the holder's U.S. federal income tax liability, if any, provided that the required information is timely furnished to the IRS.

Foreign Accounts

A U.S. federal withholding tax of 30% may apply to dividends, the gross proceeds of a disposition of our common stock, and certain "pass-thru" payments paid to a "foreign financial institution" (as specially defined under applicable rules) unless such institution enters into an agreement with the U.S. government to withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding certain U.S. account holders of such institution (which includes certain equity and debt holders of such institution, as well as certain account holders that are foreign entities with U.S. owners). This U.S. federal withholding tax of 30% will also apply to payments of dividends and, with respect to payments made on or after January 1, 2019, the gross proceeds of a disposition of our common stock paid to a "non-financial foreign entity" (as specially defined under applicable rules) unless such entity either certifies it does not have any substantial U.S. owners or provides the withholding agent with a certification identifying substantial direct and indirect U.S. owners of the entity. The withholding tax described above will not apply if the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from the rules. Under certain circumstances, a Non-U.S. Holder might be eligible for refunds or credits of such taxes. The United States has entered into agreements with certain countries that modify these general rules for

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entities located in those countries. Prospective investors are encouraged to consult with their tax advisors regarding the possible implications of these withholding provisions on their investment in our common stock.

The withholding provisions described above currently apply to payments of dividends and will generally apply to payments of gross proceeds from a sale or other disposition of our common stock on or after January 1, 2019.

UNDERWRITING

Ladenburg Thalmann & Co. Inc. is acting as the underwriter and sole book-running manager of the offering. Subject to the terms and conditions set forth in an underwriting agreement between us and the underwriter, we have agreed to sell to the underwriter, and the underwriter has agreed to purchase from us, shares of our common stock.

Subject to the terms and conditions set forth in the underwriting agreement, the underwriter has agreed to purchase all of the shares sold under the underwriting agreement (other than those covered by the underwriter's option to purchase additional shares described below) if any of these shares are purchased.

We have agreed to indemnify the underwriter against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriter may be required to make in respect of those liabilities.

The underwriter is offering the shares, subject to prior sale, when, as and if issued to and accepted by it, subject to approval of legal matters by its counsel, including the validity of the shares, and other conditions contained in the underwriting agreement, such as the receipt by the underwriter of officers' certificates and legal opinions. The underwriter reserves the right to withdraw, cancel, or modify offers to the public and to reject orders in whole or in part.

Discounts and Commissions

The underwriter has advised us that it proposes initially to offer the shares to the public at the public offering price set forth on the cover page of this prospectus supplement and to dealers at that price less a concession not in excess of \$ _____ per share. After the initial offering, the public offering price, concession, or any other term of the offering may be changed.

The following table shows the public offering price, underwriting discount, and proceeds before expenses to us. The information assumes either no exercise or full exercise by the underwriter of its option to purchase additional shares.

	Per share	Total	
		No exercise	Full exercise
Public offering price	\$ _____	\$ _____	\$ _____
Underwriting discounts and commissions	\$ _____	\$ _____	\$ _____
Proceeds, before expenses, to us	\$ _____	\$ _____	\$ _____

Our portion of the expenses of the offering, other than the underwriting discounts and commissions referred to above, is estimated at \$ _____. In addition, we have agreed to reimburse the underwriter for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority, Inc. in an amount not to exceed \$ _____.

Option to Purchase Additional Shares

We have granted an option to the underwriter, exercisable for 30 days after the date of this prospectus supplement, to purchase up to _____ additional shares from us at the public offering price, less underwriting discounts and commissions.

No Sales of Similar Securities

We and our executive officers and directors have agreed not to sell or transfer any common stock or securities convertible into or exchangeable or exercisable for common stock, for 90 days after the date of this prospectus supplement, without first obtaining the written consent of the underwriter.

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Specifically, we and these other persons have agreed, with certain limited exceptions, not to directly or indirectly:

- sell, offer, contract or grant any option to sell (including any short sale); grant any option, right or warrant to purchase; pledge; transfer; establish an open "put equivalent position" within the meaning of Rule 16a-1(h) under the Exchange Act with respect to; lend; or otherwise dispose of any common stock, options, rights, or warrants to acquire common stock;
- request or demand that we file a registration statement related to the common stock; or
- enter into any swap or other arrangement that transfers, in whole or in part, directly or indirectly, the economic consequence of ownership of any common stock.

This restriction applies to common stock and to securities convertible into or exchangeable or exercisable for common stock. It also applies to common stock owned now or acquired later by the person executing the agreement or for which the person executing the agreement later acquires the power of disposition.

The NASDAQ Global Market Listing

The shares are listed on The NASDAQ Global Market under the symbol "AXSM."

Price Stabilization, Short Positions

Until the distribution of the shares is completed, SEC rules may limit the underwriter and selling group members from bidding for and purchasing our common stock. However, the underwriter may engage in transactions that stabilize the price of the common stock, such as bids or purchases to peg, fix, or maintain that price.

In connection with the offering, the underwriter may purchase and sell our common stock in the open market. These transactions may include short sales and purchases on the open market to cover positions created by short sales. Short sales involve the sale by the underwriter of a greater number of shares than they are required to purchase in the offering. "Covered" short sales are sales made in an amount not greater than the underwriter's option to purchase additional shares described above. The underwriter may close out any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriter will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option granted to them. "Naked" short sales are sales in excess of such option. The underwriter must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriter is concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of shares of common stock made by the underwriter in the open market prior to the completion of the offering.

Similar to other purchase transactions, the underwriter's purchases to cover short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. The underwriter may conduct these transactions on The NASDAQ Global Market, in the over-the-counter market, or otherwise.

Neither we nor the underwriter makes any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor the underwriter makes any representation that the underwriter will

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engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

Electronic Distribution

In connection with the offering, the underwriter may distribute prospectuses by electronic means, such as e-mail.

Other Relationships

The underwriter and certain of its affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing, and brokerage activities. The underwriter and certain of its affiliates have engaged in, and may in the future engage in, investment banking and other commercial dealings in the ordinary course of business with us or our affiliates, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their business activities, the underwriter and its affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriter and its affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

LEGAL MATTERS

The validity of the common stock being offered in this offering will be passed upon for us by Morgan, Lewis & Bockius LLP, New York, New York. Certain legal matters related to this offering will be passed upon for the underwriter by Orrick, Herrington & Sutcliffe LLP, New York, New York.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2016, as set forth in their report, which is incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus supplement and the accompanying prospectus form part of a registration statement on Form S-3 that we filed with the SEC. This prospectus supplement and the accompanying prospectus do not contain all of the information set forth in the registration statement and the exhibits to the registration statement or the documents incorporated by reference herein and therein. For further information with respect to us and the securities that we are offering under this prospectus supplement, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement and the documents incorporated by reference herein and therein. You should rely only on the information contained in this prospectus supplement or the accompanying prospectus or incorporated by reference herein or therein. We have not authorized anyone else to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front page of this prospectus supplement, regardless of the time of delivery of this prospectus supplement or any sale of the securities offered hereby.

We file annual, quarterly, and other reports, proxy and information statements, and other information with the Securities and Exchange Commission. Copies of these materials may be inspected and copied at the public reference facilities maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of its public reference room. The SEC maintains a website that contains reports, proxy statements and other information regarding us. The address of the SEC website is www.sec.gov. We maintain a website at www.axsome.com. Information contained on our website is not incorporated into this prospectus supplement and you should not consider information contained on our website to be part of this prospectus supplement.

INFORMATION INCORPORATED BY REFERENCE

The SEC allows us to incorporate by reference into this prospectus supplement and the accompanying prospectus certain information we file with it, which means that we can disclose important information by referring you to those documents. The information incorporated by reference is considered to be a part of this prospectus supplement and the accompanying prospectus, and information that we file later with the SEC will automatically update and supersede information contained in this prospectus supplement and the accompanying prospectus.

The following documents are incorporated by reference into this document:

- our annual report on Form 10-K for the fiscal year ended December 31, 2016 filed with the SEC on March 7, 2017;
- our current reports on Form 8-K filed with the SEC on January 4, 2017, January 12, 2017, February 10, 2017, February 14, 2017, and March 14, 2017; and
- our description of our common stock contained in the registration statement on Form 8-A, filed on November 16, 2015, and all amendments and reports updating such description.

We also incorporate by reference into this prospectus all documents (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items) that are filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement and until the completion or termination of the offering. These documents include periodic reports, such as Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K, as well as proxy statements.

Any statement contained herein or in a document incorporated or deemed to be incorporated by reference into this document will be deemed to be modified or superseded for purposes of the document to the extent that a statement contained in this document or any other subsequently filed document that is deemed to be incorporated by reference into this document modifies or supersedes the statement.

We make available, free of charge, through our website 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 Section 13(a), 13(c), 14 or 15(d) of the Exchange Act as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. You may also obtain, free of charge, a copy of any of these documents (other than exhibits to these documents unless the exhibits are specifically incorporated by reference into these documents or referred to in this prospectus) by writing or calling us at the following address and telephone number:

Axsome Therapeutics, Inc.
25 Broadway
9th Floor
New York, New York 10004
(212) 332-3241

AXSOME

THERAPEUTICS

\$150,000,000

AXSOME THERAPEUTICS, INC.

**Common Stock
Preferred Stock
Warrants
Debt Securities
Rights to Purchase Common Stock, Preferred Stock,
Debt Securities or Units
Units**

We may offer and sell from time to time our shares of common stock, shares of preferred stock, warrants, debt securities and rights to purchase common stock, preferred stock, debt securities or units, as well as units that include any of these securities. We may sell any combination of these securities in one or more offerings with an aggregate initial offering price of up to \$150,000,000.

This prospectus provides you with a general description of the securities we may offer. Each time we offer securities pursuant to this prospectus, we will provide a prospectus supplement containing specific terms of the particular offering together with this prospectus. You should read this prospectus and the applicable prospectus supplement carefully before you invest in any securities. The prospectus supplement also may add, update or change information contained in this prospectus. This prospectus may not be used to offer and sell securities unless accompanied by the applicable prospectus supplement.

Our common stock is listed on the NASDAQ Capital Market under the symbol "AXSM." On November 30, 2016, the closing price of our common stock was \$6.55.

Investing in our securities involves significant risks. We strongly recommend that you read carefully the risks we describe in this prospectus and in any accompanying prospectus supplement, as well as the risk factors that are incorporated by reference into this prospectus from our filings made with the Securities and Exchange Commission. See "Risk Factors" on page 5 of this prospectus.

We may sell the securities directly to investors, or to or through underwriters or dealers, and also to other purchasers or through agents. The names of any underwriters or agents that are included in a sale of securities to you, and any applicable commissions or discounts, will be stated in an accompanying prospectus supplement. In addition, the underwriters, if any, may over-allot a portion of the securities.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is December 16, 2016

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a "shelf" registration process. Under this shelf registration process, we may offer and sell from time to time any combination of the securities described in this prospectus in one or more offerings in amounts, at prices and on terms that we determine at the time of the offering, with an aggregate initial offering price of up to \$150,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we offer securities under this registration statement we will provide a prospectus supplement that describes the terms of the relevant offering. The prospectus supplement also may add, update or change information contained in this prospectus. Before making an investment decision, you should read carefully both this prospectus and any prospectus supplement together with the documents incorporated by reference into this prospectus as described below under the heading "Information Incorporated by Reference."

The registration statement that contains this prospectus, including the exhibits to the registration statement and the information incorporated by reference, provides additional information about us and our securities. That registration statement can be read at the SEC website (www.sec.gov) or at the SEC public reference room, as discussed below under the heading "Where You Can Find More Information."

You should rely only on the information provided in the registration statement, this prospectus and in any prospectus supplement, including the information incorporated by reference. We have not authorized anyone to provide you with different information. You should not assume that the information in this prospectus or any supplement to this prospectus is accurate at any date other than the date indicated on the cover page of these documents or the filing date of any document incorporated by reference, regardless of its time of delivery. We are not making an offer to sell the securities in any jurisdiction where the offer or sale is not permitted.

We may sell our securities to or through underwriters, initial purchasers, dealers or agents, directly to purchasers or through a combination of any of these methods of sale, as designated from time to time. We and our agents reserve the sole right to accept or reject in whole or in part any proposed purchase of our securities. An applicable prospectus supplement, which we will provide each time we offer the securities, will set forth the names of any underwriters, initial purchasers, dealers or agents involved in the sale of our securities, and any related fee, commission or discount arrangements. See "Plan of Distribution."

The terms "Axsome," the "Company," "our," "us" and "we," as used in this prospectus, refer to Axsome Therapeutics, Inc., unless we state otherwise or the context indicates otherwise.

AXSOME THERAPEUTICS, INC.

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 two late stage candidates, AXS-02 and AXS-05, which we are developing for multiple indications. We have initiated a Phase 3 trial with AXS-02 in complex regional pain syndrome, or CRPS, which we refer to as the CREATE-1 study, and 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 have also initiated a Phase 3 trial with AXS-05 in treatment resistant depression, or TRD, which we refer to as the STRIDE-1 study, and plan to initiate a Phase 2/3 trial in agitation in patients with Alzheimer's disease, or AD. 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.

Our first product candidate, 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 three conditions: CRPS; knee OA associated with BMLs; and chronic low back pain, or CLBP, associated with type 1 or mixed type 1 and type 2 Modic changes, or 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 U.S. Food and Drug Administration, or FDA, approval for AXS-02 utilizing the 505(b)(2) regulatory development pathway. AXS-02 has been granted Orphan Drug Designation by the FDA and Orphan Medicinal Product Designation by the EMA for the treatment of CRPS.

Our second product candidate, AXS-05, is an innovative fixed-dose combination of dextromethorphan, or DM, and bupropion. We are developing AXS-05 initially for the treatment of the following two conditions: TRD and agitation in patients with AD. 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.

We have one active program, AXS-06, in preclinical development. We are developing AXS-06 for the treatment of chronic pain disorders.

Our principal executive offices are located at 25 Broadway, 9th Floor, New York, New York 10004, and our telephone number is (212) 332-3241. Our website address is www.axsome.com. The information contained on our website is not incorporated by reference into this prospectus, and you should not consider any information contained on, or that can be accessed through, our website as part of this prospectus or in deciding whether to purchase our securities.

Our filings with the SEC are posted on our website at www.axsome.com. The information found on our website is not part of this or any other report we file with or furnish to the SEC. The public can also obtain copies of these filings by visiting the SEC's Public Reference Room at 100 F Street NE, Washington DC 20549, or by calling the SEC at 1-800-SEC-0330 or by accessing the SEC's website at www.sec.gov.

FORWARD-LOOKING STATEMENTS

From time to time, in reports filed with the Securities and Exchange Commission (including this registration statement), in press releases and in other communications to stockholders or the investment community, we may provide forward-looking statements concerning possible or anticipated future results of operations or business developments. These statements are based on our management's current expectations or predictions of future conditions, events or results based on various assumptions and our management's estimates of trends and economic factors in the markets in which we are active, as well as our business plans. Words such as "expects," "anticipates," "intends,"

"plans," "believes," "seeks," "estimates," "projects," "forecasts," "may," "should," and variations of such words and similar expressions are intended to identify such forward-looking statements. The forward-looking statements may include, without limitation, statements regarding product candidate development, product candidate potential, regulatory environment, sales and marketing strategies, capital resources or operating performance. The forward-looking statements are subject to risks and uncertainties, which may cause results to differ materially from those set forth in the statements. Forward-looking statements in this registration statement should be evaluated together with the many uncertainties that affect our business and our market, particularly those discussed in the "Risk Factors" section of our Annual Report on Form 10-K for the year ended December 31, 2015, as amended, and our subsequent filings, which are incorporated by reference into this prospectus, to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements. Forward-looking statements are not guarantees of future performance, and actual results may differ materially from those projected. The forward-looking statements are representative only as of the date of this prospectus and except as required by law, we assume no responsibility to update any forward-looking statements, whether as a result of new information, future events or otherwise.

You should read this prospectus and the documents that we reference in this prospectus and have been filed as exhibits to the registration statement of which this prospectus is a part completely and with the understanding that our actual future results may be materially different from what we expect. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any issuance or sale of our common shares. Except as required by law, we do not assume any obligation to update any forward-looking statements.

RISK FACTORS

Investing in our securities involves risk. You should carefully consider the specific risks discussed or incorporated by reference into the applicable prospectus supplement, together with all the other information contained in the prospectus supplement or incorporated by reference into this prospectus and the applicable prospectus supplement. You should also consider the risks, uncertainties and assumptions discussed under the caption "Risk Factors" included in our Annual Report on Form 10-K for the year ended December 31, 2015, as amended, and in subsequent filings, which are incorporated by reference into this prospectus. These risk factors may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future or by a prospectus supplement relating to a particular offering of our securities. These risks and uncertainties are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us, or that we currently view as immaterial, may also impair our business. If any of the risks or uncertainties described in our SEC filings or any prospectus supplement or any additional risks and uncertainties actually occur, our business, financial condition and results of operations could be materially and adversely affected. In that case, the trading price of our securities could decline and you might lose all or part of your investment.

RATIO OF EARNINGS TO FIXED CHARGES AND PREFERRED STOCK DIVIDEND REQUIREMENTS

The following table sets forth our ratio of earnings to fixed charges and our ratio of earnings to combined fixed charges and preferred stock dividends for each of the periods indicated. You should read this table in conjunction with the financial statements and notes incorporated by reference in this registration statement.

	Nine Months Ended September 30, 2016	Year Ended December 31, 2015	Year Ended December 31, 2014	Year Ended December 31, 2013
Ratios of earnings to fixed charges(1)(2)	—	—	—	—
Ratios of earnings to combined fixed charges and preferred stock dividends(1)(2)	—	—	—	—

- (1) Due to our losses for the nine months ended September 30, 2016 and the years ended December 31, 2015, 2014 and 2013, the coverage ratio was less than 1:1.
- (2) We would have needed to generate additional earnings of \$19.9 million, \$12.2 million, \$6.0 million and \$2.2 million for the nine months ended September 30, 2016 and the years ended December 31, 2015, 2014 and 2013, respectively, to cover our fixed charges and our combined fixed charges and preferred stock dividends in those periods.

USE OF PROCEEDS

Unless otherwise indicated in the applicable prospectus supplement, we will use the net proceeds from the sale of the securities offered hereby for general corporate purposes, which include, but are not limited to funding the ongoing clinical development of our product candidates, general and administrative expenses or other corporate obligations. We may use a portion of the net proceeds to pay off outstanding indebtedness, if any, or acquire or invest in businesses, products and technologies.

DESCRIPTION OF CAPITAL STOCK

The following description is a general summary of the terms of the shares of common stock or shares of preferred stock that we may issue. The description below and in any prospectus supplement does not include all of the terms of the shares of common stock or shares of preferred stock and should be read together with our Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws, copies of which have been filed previously with the SEC. For more information on how you can obtain copies of our Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws, see "Where You Can Find More Information."

Common Stock

General

Our Amended and Restated Certificate of Incorporation provides the authority to issue 150,000,000 shares of common stock, par value \$0.0001 per share. At November 28, 2016, there were 19,153,417 shares of common stock outstanding. Each share of our common stock has the same relative rights and is identical in all respects to each other share of our common stock. The rights, preferences and privileges of holders of our common stock are subject to the rights, preferences and privileges of the holders of shares of any series of preferred stock that we have issued or may issue in the future.

Voting Rights

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

Dividends

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

Liquidation Rights

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

Miscellaneous

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

NASDAQ Listing

Our common stock is listed on the NASDAQ Capital Market under the symbol "AXSM."

Transfer Agent and Registrar

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

Preferred Stock**General**

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

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

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

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

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

If we issue shares of preferred stock under this prospectus and any related prospectus supplement, the shares will be fully paid and non-assessable and will not have, or be subject to, any preemptive or similar rights.

Voting Rights

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

Transfer Agent and Registrar

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

Other

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

Delaware Law and Certain Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws Provisions

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

- Authorize the issuance of preferred stock which can be created and issued by the board of directors without prior stockholder approval, with rights senior to those of our common stock;
- Provide for a classified board of directors, with each director serving a staggered three-year term;
- Prohibit our stockholders from filling board vacancies, calling special stockholder meetings or taking action by written consent;
- Provide for the removal of a director only with cause and by the affirmative vote of the holders of 66²/3% or more of the shares then entitled to vote at an election of our directors;
- Require advance written notice of stockholder proposals and director nominations; and
- Require any action instituted against our officers or directors in connection with their service to us to be brought in the state of Delaware.

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

Indemnification

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

DESCRIPTION OF WARRANTS

We may issue warrants for the purchase of shares of our common stock, shares of our preferred stock or debt securities. The following description sets forth certain general terms and provisions of the warrants that we may offer pursuant to this prospectus. The particular terms of the warrants and the extent, if any, to which the general terms and provisions may apply to the warrants so offered will be described in the applicable prospectus supplement.

Warrants may be issued independently or together with other securities and may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and a bank or trust company, as warrant agent. The warrant agent will act solely as our agent in connection with the warrants and will not have any obligation or relationship of agency or trust for or with any holders or beneficial owners of warrants.

A copy of the forms of the warrant agreement and the warrant certificate relating to any particular issue of warrants will be filed with the SEC each time we issue warrants, and you should read those documents for provisions that may be important to you. For more information on how you can obtain copies of the forms of the warrant agreement and the related warrant certificate, see "Where You Can Find More Information."

Stock Warrants

The prospectus supplement relating to a particular issue of warrants to issue shares of our common stock or shares of our preferred stock will describe the terms of the common share warrants and preferred share warrants, including the following:

- the title of the warrants;
- the offering price for the warrants, if any;
- the aggregate number of the warrants;
- the designation and terms of the shares of common stock or shares of preferred stock that may be purchased upon exercise of the warrants;
- the terms for changes or adjustments to the exercise price of the warrants;
- if applicable, the designation and terms of the securities that the warrants are issued with and the number of warrants issued with each security;
- if applicable, the date from and after which the warrants and any securities issued with the warrants will be separately transferable;
- the number of shares of common stock or shares of preferred stock that may be purchased upon exercise of a warrant and the price at which the shares may be purchased upon exercise;
- the dates on which the right to exercise the warrants commence and expire;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, a discussion of material United States federal income tax considerations;
- anti-dilution provisions of the warrants, if any;
- redemption or call provisions, if any, applicable to the warrants;

- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants; and
- any other information we think is important about the warrants.

Debt Warrants

The prospectus supplement relating to a particular issue of warrants to issue debt securities will describe the terms of those warrants, including the following:

- the title of the warrants;
- the offering price for the warrants, if any;
- the aggregate number of the warrants;
- the designation and terms of the debt securities purchasable upon exercise of the warrants;
- the terms for changes or adjustments to the exercise price of the warrants;
- if applicable, the designation and terms of the debt securities that the warrants are issued with and the number of warrants issued with each debt security;
- if applicable, the date from and after which the warrants and any debt securities issued with them will be separately transferable;
- the principal amount of debt securities that may be purchased upon exercise of a warrant and the price at which the debt securities may be purchased upon exercise;
- the dates on which the right to exercise the warrants will commence and expire;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- whether the warrants represented by the warrant certificates or debt securities that may be issued upon exercise of the warrants will be issued in registered or bearer form;
- information relating to book-entry procedures, if any;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, a discussion of material United States federal income tax considerations;
- anti-dilution provisions of the warrants, if any;
- redemption or call provisions, if any, applicable to the warrants;
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants; and
- any other information we think is important about the warrants.

Exercise of Warrants

Each warrant will entitle the holder of the warrant to purchase at the exercise price set forth in the applicable prospectus supplement the number of shares of common stock, shares of preferred stock or the principal amount of debt securities being offered. Holders may exercise warrants at any time up to the close of business on the expiration date set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants are void. Holders may exercise warrants as set forth in the prospectus supplement relating to the warrants being offered.

Until a holder exercises the warrants to purchase our shares of common stock, shares of preferred stock or debt securities, the holder will not have any rights as a holder of our shares of common stock, shares of preferred stock or debt securities, as the case may be, by virtue of ownership of warrants.

DESCRIPTION OF DEBT SECURITIES

The following is a general description of the terms of debt securities we may issue from time to time unless we provide otherwise in the applicable prospectus supplement. Particular terms of any debt securities we offer will be described in the prospectus supplement relating to such debt securities.

As required by Federal law for all bonds and notes of companies that are publicly offered, any debt securities we issue will be governed by a document called an "indenture," the form of which is filed as an exhibit to the registration statement of which this prospectus forms a part. We have summarized the general features of the debt securities to be governed by the indenture. The summary is not complete. An indenture is a contract between us and a financial institution acting as trustee on behalf of the holders of the debt securities, and is subject to and governed by the Trust Indenture Act of 1939, as amended. The trustee has two main roles. First, the trustee can enforce holders' rights against us if we default. There are some limitations on the extent to which the trustee acts on holders' behalf, described in the second paragraph under "Description of Debt Securities—Events of Default." Second, the trustee performs certain administrative duties, such as sending interest and principal payments to holders.

Because this section is a summary, it does not describe every aspect of any debt securities we may issue or the indenture governing any such debt securities. Particular terms of any debt securities we offer will be described in the prospectus supplement relating to such debt securities, and we urge you to read the applicable executed indenture, which will be filed with the SEC at the time of any offering of debt securities, because it, and not this description, will define the rights of holders of such debt securities.

A prospectus supplement will describe the particular terms of any series of debt securities we may issue, including some or all of the following:

- the designation or title of the series of debt securities;
- the total principal amount of the series of debt securities, the denominations in which the offered debt securities will be issued and whether the offering may be reopened for additional securities of that series and on what terms;
- the percentage of the principal amount at which the series of debt securities will be offered;
- the date or dates on which principal will be payable;
- the rate or rates (which may be either fixed or variable) and/or the method of determining such rate or rates of interest, if any;
- the date or dates from which any interest will accrue, or the method of determining such date or dates, and the date or dates on which any interest will be payable;
- the terms for redemption, extension or early repayment, if any;
- the currencies in which the series of debt securities are issued and payable;
- whether the amount of payments of principal, interest or premium, if any, on a series of debt securities will be determined with reference to an index, formula or other method and how these amounts will be determined;
- the place or places of payment, transfer, conversion and/or exchange of the debt securities;
- the provision for any sinking fund;

- any restrictive covenants;
- events of default;
- whether the series of debt securities are issuable in certificated form;
- any provisions for legal defeasance or covenant defeasance;
- whether and under what circumstances we will pay additional amounts in respect of any tax, assessment or governmental charge and, if so, whether we will have the option to redeem the debt securities rather than pay the additional amounts (and the terms of this option);
- any provisions for convertibility or exchangeability of the debt securities into or for any other securities;
- whether the debt securities are subject to subordination and the terms of such subordination;
- any listing of the debt securities on any securities exchange;
- if applicable, a discussion of certain U.S. Federal income tax considerations, including those related to original issue discount, if applicable; and
- any other material terms.

The debt securities may be secured or unsecured obligations. Unless the prospectus supplement states otherwise, principal, interest and premium, if any, will be paid by us in immediately available funds.

General

The indenture may provide that any debt securities proposed to be sold under this prospectus and the applicable prospectus supplement relating to such debt securities ("offered debt securities") and any debt securities issuable upon conversion or exchange of other offered securities ("underlying debt securities") may be issued under the indenture in one or more series.

For purposes of this prospectus, any reference to the payment of principal of, or interest or premium, if any, on, debt securities will include additional amounts if required by the terms of the debt securities.

Debt securities issued under an indenture, when a single trustee is acting for all debt securities issued under the indenture, are called the "indenture securities." The indenture may also provide that there may be more than one trustee thereunder, each with respect to one or more different series of securities issued thereunder. See "Description of Debt Securities—Resignation of Trustee" below. At a time when two or more trustees are acting under an indenture, each with respect to only certain series, the term "indenture securities" means the one or more series of debt securities with respect to which each respective trustee is acting. In the event that there is more than one trustee under an indenture, the powers and trust obligations of each trustee described in this prospectus will extend only to the one or more series of indenture securities for which it is trustee. If two or more trustees are acting under an indenture, then the indenture securities for which each trustee is acting would be treated as if issued under separate indentures.

We refer you to the applicable prospectus supplement relating to any debt securities we may issue from time to time for information with respect to any deletions from, modifications of or additions to the Events of Default or covenants that are described below, including any addition of a covenant or other provision providing event risk or similar protection, that will be applicable with respect to such debt securities.

We have the ability to issue indenture securities with terms different from those of indenture securities previously issued and, without the consent of the holders thereof, to reopen a previous issue of a series of indenture securities and issue additional indenture securities of that series unless the reopening was restricted when that series was created.

Conversion and Exchange

If any debt securities are convertible into or exchangeable for other securities, the related prospectus supplement will explain the terms and conditions of the conversion or exchange, including the conversion price or exchange ratio (or the calculation method), the conversion or exchange period (or how the period will be determined), if conversion or exchange will be mandatory or at the option of the holder or us, provisions for adjusting the conversion price or the exchange ratio and provisions affecting conversion or exchange in the event of the redemption of the underlying debt securities. These terms may also include provisions under which the number or amount of other securities to be received by the holders of the debt securities upon conversion or exchange would be calculated according to the market price of the other securities as of a time stated in the prospectus supplement.

Payment and Paying Agents

We will pay interest to the person listed in the applicable trustee's records as the owner of the debt security at the close of business on a particular day in advance of each due date for interest, even if that person no longer owns the debt security on the interest due date. That day, often approximately two weeks in advance of the interest due date, is called the "record date." Because we will pay all the interest for an interest period to the holders on the record date, holders buying and selling debt securities must work out between themselves the appropriate purchase price. The most common manner is to adjust the sales price of the debt securities to prorate interest fairly between buyer and seller based on their respective ownership periods within the particular interest period. This prorated interest amount is called "accrued interest."

Events of Default

Holders of debt securities of any series will have rights if an Event of Default occurs in respect of the debt securities of such series and is not cured, as described later in this subsection. The term "Event of Default" in respect of the debt securities of any series means any of the following:

- we do not pay the principal of, or any premium on, a debt security of the series on its due date;
- we do not pay interest on a debt security of the series within 30 days of its due date;
- we do not deposit any sinking fund payment in respect of debt securities of the series on its due date and we do not cure this default within five days;
- we remain in breach of a covenant in respect of debt securities of the series for 90 days after we receive a written notice of default stating we are in breach. The notice must be sent by either the trustee or holders of at least 25% of the principal amount of debt securities of the series;
- we file for bankruptcy or certain other events of bankruptcy, insolvency or reorganization occur; and
- any other Event of Default occurs in respect of debt securities of the series described in the prospectus supplement.

An Event of Default for a particular series of debt securities does not necessarily constitute an Event of Default for any other series of debt securities issued under the same or any other indenture. The trustee may withhold notice to the holders of debt securities of any default, except in the payment of principal, premium or interest, if it considers the withholding of notice to be in the best interests of the holders.

Remedies if an Event of Default Occurs

If an Event of Default has occurred and has not been cured or waived, the trustee or the holders of not less than 25% in principal amount of the debt securities of the affected series may declare the entire principal amount of all the debt securities of that series to be due and immediately payable. This is called a declaration of acceleration of maturity. A declaration of acceleration of maturity may be canceled by the holders of a majority in principal amount of the debt securities of the affected series if the default is cured or waived and certain other conditions are satisfied.

Except in cases of default, where the trustee has some special duties, the trustee typically is not required to take any action under an indenture at the request of any holders unless the holders offer the trustee reasonable protection from expenses and liability (called an "indemnity"). If reasonable indemnity is provided, the holders of a majority in principal amount of the outstanding debt securities of the relevant series may direct the time, method and place of conducting any lawsuit or other formal legal action seeking any remedy available to the trustee. The trustee may refuse to follow those directions in certain circumstances.

Before a holder is allowed to bypass the trustee and bring its own lawsuit or other formal legal action or take other steps to enforce its rights or protect its interests relating to any debt securities, the following must occur:

- the holder must give the trustee written notice that an Event of Default has occurred and remains uncured;
- the holders of at least 25% in principal amount of all outstanding debt securities of the relevant series must make a written request that the trustee take action because of the default and must offer reasonable indemnity to the trustee against the cost and other liabilities of taking that action;
- the trustee must not have taken action for 60 days after receipt of the above notice and offer of indemnity; and
- the holders of a majority in principal amount of the debt securities must not have given the trustee a direction inconsistent with the above notice during that 60-day period.

However, a holder is entitled at any time to bring a lawsuit for the payment of money due on its debt securities on or after the due date. Each year, we will furnish to each trustee a written statement of certain of our officers certifying that to their knowledge we are in compliance with the indenture and the debt securities, or else specifying any default.

Waiver of Default

The holders of a majority in principal amount of the relevant series of debt securities may waive a default for all such series of debt securities. If this happens, the default will be treated as if it had not occurred. No one can waive a payment default on a holder's debt security, however, without the holder's approval.

Merger or Consolidation

Under the terms of an indenture, we may be permitted to consolidate or merge with another entity. We may also be permitted to sell all or substantially all of our assets to another entity. However, typically we may not take any of these actions unless all the following conditions are met:

- if we do not survive such transaction or we convey, transfer or lease our properties and assets substantially as an entirety, the acquiring company must be a corporation, limited liability company, partnership or trust, or other corporate form, organized under the laws of any state of

the United States or the District of Columbia, and such company must agree to be legally responsible for our debt securities, and, if not already subject to the jurisdiction of any state of the United States or the District of Columbia, the new company must submit to such jurisdiction for all purposes with respect to the debt securities and appoint an agent for service of process;

- alternatively, we must be the surviving company;
- immediately after the transaction no Event of Default will exist;
- we must deliver certain certificates and documents to the trustee; and
- we must satisfy any other requirements specified in the prospectus supplement relating to a particular series of debt securities.

Modification or Waiver

There are three types of changes we may make to an indenture and the debt securities issued thereunder.

Changes Requiring Approval

First, there are changes that we cannot make to debt securities without specific approval of all of the holders. The following is a list of the types of changes that may require specific approval:

- change the stated maturity of the principal or rate of interest on a debt security;
- reduce any amounts due on a debt security;
- reduce the amount of principal payable upon acceleration of the maturity of a security following a default;
- at any time after a change of control has occurred, reduce any premium payable upon a change of control;
- change the place or currency of payment on a debt security (except as otherwise described in the prospectus or prospectus supplement);
- impair the right of holders to sue for payment;
- adversely affect any right to convert or exchange a debt security in accordance with its terms;
- reduce the percentage of holders of debt securities whose consent is needed to modify or amend the indenture;
- reduce the percentage of holders of debt securities whose consent is needed to waive compliance with certain provisions of the indenture or to waive certain defaults;
- modify any other aspect of the provisions of the indenture dealing with supplemental indentures, modification and waiver of past defaults, changes to the quorum or voting requirements or the waiver of certain covenants; and
- change any obligation we have to pay additional amounts.

Changes Not Requiring Approval

The second type of change does not require any vote by the holders of the debt securities. This type is limited to clarifications and certain other changes that would not adversely affect holders of the outstanding debt securities in any material respect, including the addition of covenants and guarantees. We also do not need any approval to make any change that affects only debt securities to be issued under the indenture after the change takes effect.

Changes Requiring Majority Approval

Any other change to the indenture and the debt securities may require the following approval:

- if the change affects only one series of debt securities, it must be approved by the holders of a majority in principal amount of that series; and
- if the change affects more than one series of debt securities issued under the same indenture, it must be approved by the holders of a majority in principal amount of all of the series affected by the change, with all affected series voting together as one class for this purpose.

The holders of a majority in principal amount of all of the series of debt securities issued under an indenture, voting together as one class for this purpose, may waive our compliance obligations with respect to some of our covenants in that indenture. However, we cannot obtain a waiver of a payment default or of any of the matters covered by the bullet points included above under "Description of Debt Securities—Modification or Waiver—Changes Requiring Approval."

Further Details Concerning Voting

When taking a vote on proposed changes to the indenture and the debt securities, we expect to use the following rules to decide how much principal to attribute to a debt security:

- for original issue discount securities, we will use the principal amount that would be due and payable on the voting date if the maturity of these debt securities were accelerated to that date because of a default;
- for debt securities whose principal amount is not known (for example, because it is based on an index), we will use a special rule for that debt security described in the related prospectus supplement; and
- for debt securities denominated in one or more foreign currencies, we will use the U.S. dollar equivalent.

Debt securities will not be considered outstanding, and therefore not eligible to vote, if we have deposited or set aside in trust money for their payment or redemption. Debt securities will also not be eligible to vote if they have been fully defeased as described later under "Description of Debt Securities—Defeasance—Legal Defeasance."

We generally will be entitled to set any day as a record date for the purpose of determining the holders of outstanding indenture securities that are entitled to vote or take other action under the indenture. If we set a record date for a vote or other action to be taken by holders of one or more series, that vote or action may be taken only by persons who are holders of outstanding indenture securities of those series on the record date and must be taken within 11 months following the record date.

Book-entry and other indirect holders will need to consult their banks or brokers for information on how approval may be granted or denied if we seek to change the indenture or the debt securities or request a waiver.

Defeasance

The following provisions will be applicable to each series of debt securities unless we state in the applicable prospectus supplement that the provisions of covenant defeasance and legal defeasance will not be applicable to that series.

Covenant Defeasance

We can make the deposit described below and be released from some of the restrictive covenants in the indenture under which the particular series was issued. This is called "covenant defeasance." In that event, the holders would lose the protection of those restrictive covenants but would gain the protection of having money and government securities set aside in trust to repay holders' debt securities. If applicable, a holder also would be released from the subordination provisions described under "Description of Debt Securities—Indenture Provisions—Subordination" below. In order to achieve covenant defeasance, we must do the following:

- If the debt securities of the particular series are denominated in U.S. dollars, we must deposit in trust for the benefit of all holders of such debt securities a combination of money and U.S. government or U.S. government agency notes or bonds that will generate enough cash to make interest, principal and any other payments on the debt securities on their various due dates;
- We may be required to deliver to the trustee a legal opinion of our counsel confirming that, under current U.S. Federal income tax law, we may make the above deposit without causing the holders to be taxed on the debt securities any differently than if we did not make the deposit and just repaid the debt securities ourselves at maturity; and
- We must deliver to the trustee certain documentation stating that all conditions precedent to covenant defeasance have been complied with.

If we accomplish covenant defeasance, holders can still look to us for repayment of the debt securities if there were a shortfall in the trust deposit or the trustee is prevented from making payment. In fact, if one of the remaining Events of Default occurred (such as our bankruptcy) and the debt securities became immediately due and payable, there might be a shortfall. Depending on the event causing the default, holders may not be able to obtain payment of the shortfall.

Legal Defeasance

As described below, we can legally release ourselves from all payment and other obligations on the debt securities of a particular series (called "legal defeasance"), (1) if there is a change in U.S. Federal tax law that allows us to effect the release without causing the holders to be taxed any differently than if the release had not occurred, and (2) if we put in place the following other arrangements for holders to be repaid:

- If the debt securities of the particular series are denominated in U.S. dollars, we must deposit in trust for the benefit of all holders of such debt securities a combination of money and U.S. government or U.S. government agency notes or bonds that will generate enough cash to make interest, principal and any other payments on the debt securities on their various due dates;
- We may be required to deliver to the trustee a legal opinion confirming that there has been a change in current U.S. Federal tax law or an Internal Revenue Service ruling that allows us to make the above deposit without causing the holders to be taxed on the debt securities any differently than if we did not make the deposit and just repaid the debt securities ourselves at maturity. Under current U.S. Federal tax law, the deposit and our legal release from the debt securities would be treated as though we paid each holder its share of the cash and notes or bonds at the time the cash and notes or bonds were deposited in trust in exchange for its debt securities and holders would recognize gain or loss on the debt securities at the time of the deposit; and
- We must deliver to the trustee a legal opinion and officers' certificate stating that all conditions precedent to legal defeasance have been complied with.

If we ever did accomplish legal defeasance, as described above, holders would have to rely solely on the trust deposit for repayment of the debt securities. Holders could not look to us for repayment in the unlikely event of any shortfall. Conversely, the trust deposit would most likely be protected from claims of our lenders and other creditors if we ever became bankrupt or insolvent. If applicable, holders would also be released from the subordination provisions described later under "Description of Debt Securities—Indenture Provisions—Subordination."

Resignation of Trustee

Each trustee may resign or be removed with respect to one or more series of indenture securities provided that a successor trustee is appointed to act with respect to such series. In the event that two or more persons are acting as trustee with respect to different series of indenture securities under the indenture, each of the trustees will be a trustee of a trust separate and apart from the trust administered by any other trustee.

Indenture Provisions—Subordination

Upon any distribution of our assets upon our dissolution, winding up, liquidation or reorganization, the payment of the principal of (and premium, if any) and interest on any indenture securities denominated as subordinated debt securities is to be subordinated to the extent provided in the indenture in right of payment to the prior payment in full of all Senior Indebtedness (defined below), but our obligation to holders to make payment of the principal of (and premium, if any) and interest on such subordinated debt securities will not otherwise be affected. In addition, no payment on account of principal (or premium, if any), interest or sinking fund, if any, may be made on such subordinated debt securities at any time unless full payment of all amounts due in respect of the principal (and premium, if any), interest and sinking fund, if any, on Senior Indebtedness has been made or duly provided for in money or money's worth.

In the event that, notwithstanding the foregoing, any payment from us is received by the trustee in respect of subordinated debt securities or by the holders of any of such subordinated debt securities before all Senior Indebtedness is paid in full, the payment or distribution must be paid over to the holders of the Senior Indebtedness or on their behalf for application to the payment of all the Senior Indebtedness remaining unpaid until all the Senior Indebtedness has been paid in full, after giving effect to any concurrent payment or distribution to the holders of the Senior Indebtedness. Subject to the payment in full of all Senior Indebtedness, the holders of such subordinated debt securities will be subrogated to the rights of the holders of the Senior Indebtedness to the extent of payments made to the holders of the Senior Indebtedness out of the distributive share of such subordinated debt securities.

By reason of this subordination, in the event of a distribution of our assets upon our insolvency, certain of our senior creditors may recover more, ratably, than holders of any subordinated debt securities. The related indenture will provide that these subordination provisions will not apply to money and securities held in trust under the defeasance provisions of the indenture.

"Senior Indebtedness" will be defined in an applicable indenture as the principal of (and premium, if any) and unpaid interest on:

- our indebtedness (including indebtedness of others guaranteed by us), whenever created, incurred, assumed or guaranteed, for money borrowed (other than indenture securities issued under the indenture and denominated as subordinated debt securities), unless in the instrument creating or evidencing the same or under which the same is outstanding it is provided that this indebtedness is not senior or prior in right of payment to the subordinated debt securities; and
- renewals, extensions, modifications and refinancings of any of such indebtedness.

The prospectus supplement accompanying any series of indenture securities denominated as subordinated debt securities will set forth the approximate amount of our Senior Indebtedness outstanding as of a recent date.

Trustee

We intend to name the indenture trustee for each series of indenture securities in the related prospectus supplement.

Certain Considerations Relating to Foreign Currencies

Debt securities denominated or payable in foreign currencies may entail significant risks. These risks include the possibility of significant fluctuations in the foreign currency markets, the imposition or modification of foreign exchange controls and potential illiquidity in the secondary market. These risks will vary depending upon the currency or currencies involved and will be more fully described in the applicable prospectus supplement.

DESCRIPTION OF RIGHTS

The following is a general description of the terms of the rights we may issue from time to time unless we provide otherwise in the applicable prospectus supplement. Particular terms of any rights we offer will be described in the prospectus supplement relating to such rights.

General

We may issue rights to purchase common stock, preferred stock, debt securities or units. Rights may be issued independently or together with other securities and may or may not be transferable by the person purchasing or receiving the rights. In connection with any rights offering to our stockholders, we may enter into a standby underwriting, backstop or other arrangement with one or more underwriters or other persons pursuant to which such underwriters or other persons would purchase any offered securities remaining unsubscribed for after such rights offering. In connection with a rights offering to our stockholders, we would distribute certificates evidencing the rights and a prospectus supplement to our stockholders on or about the record date that we set for receiving rights in such rights offering.

The applicable prospectus supplement will describe the following terms of any rights we may issue, including some or all of the following:

- the title and aggregate number of the rights;
- the subscription price or a formula for the determination of the subscription price for the rights and the currency or currencies in which the subscription price may be payable;
- if applicable, the designation and terms of the securities with which the rights are issued and the number of rights issued with each such security or each principal amount of such security;
- the number or a formula for the determination of the number of the rights issued to each stockholder;
- the extent to which the rights are transferable;
- in the case of rights to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one right;
- in the case of rights to purchase common stock or preferred stock, the type of stock and number of shares of stock purchasable upon exercise of one right;

- the date on which the right to exercise the rights will commence, and the date on which the rights will expire (subject to any extension);
- if applicable, the minimum or maximum amount of the rights that may be exercised at any one time;
- the extent to which such rights include an over-subscription privilege with respect to unsubscribed securities;
- if applicable, the procedures for adjusting the subscription price and number of shares of common stock or preferred stock purchasable upon the exercise of each right upon the occurrence of certain events, including stock splits, reverse stock splits, combinations, subdivisions or reclassifications of common stock or preferred stock;
- the effect on the rights of any merger, consolidation, sale or other disposition of our business;
- the terms of any rights to redeem or call the rights;
- information with respect to book-entry procedures, if any;
- the terms of the securities issuable upon exercise of the rights;
- if applicable, the material terms of any standby underwriting, backstop or other purchase arrangement that we may enter into in connection with the rights offering;
- if applicable, a discussion of certain U.S. Federal income tax considerations; and
- any other terms of the rights, including terms, procedures and limitations relating to the exchange and exercise of the rights.

Exercise of Rights

Each right will entitle the holder to purchase for cash or other consideration such shares of stock or principal amount of securities at the subscription price as shall in each case be set forth in, or be determinable as set forth in, the prospectus supplement relating to the rights offered thereby. Rights may be exercised as set forth in the applicable prospectus supplement beginning on the date specified therein and continuing until the close of business on the expiration date set forth in the prospectus supplement relating to the rights offered thereby. After the close of business on the expiration date, unexercised rights will become void.

Upon receipt of payment and a subscription certificate properly completed and duly executed at the corporate trust office of the subscription agent or any other office indicated in the prospectus supplement, we will, as soon as practicable, forward the securities purchasable upon such exercise. If less than all of the rights represented by such subscription certificate are exercised, a new subscription certificate will be issued for the remaining rights. If we so indicate in the applicable prospectus supplement, holders of the rights may surrender securities as all or part of the exercise price for rights.

We may determine to offer any unsubscribed offered securities directly to stockholders, persons other than stockholders, to or through agents, underwriters or dealers or through a combination of such methods, including pursuant to standby underwriting, backstop or other arrangements, as set forth in the applicable prospectus supplement.

Prior to exercising their rights, holders of rights will not have any of the rights of holders of the securities purchasable upon subscription, including, in the case of rights to purchase common stock or preferred stock, the right to receive dividends, if any, or payments upon our liquidation, dissolution or winding up or to exercise any voting rights or, in the case of rights to purchase debt securities, the right to receive principal, premium, if any, or interest payments, on the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture.

DESCRIPTION OF UNITS

We may issue units comprising one or more securities described in this prospectus in any combination. The following description sets forth certain general terms and provisions of the units that we may offer pursuant to this prospectus. The particular terms of the units and the extent, if any, to which the general terms and provisions may apply to the units so offered will be described in the applicable prospectus supplement.

Each unit will be issued so that the holder of the unit also is the holder of each security included in the unit. Thus, the unit will have the rights and obligations of a holder of each included security. Units will be issued pursuant to the terms of a unit agreement, which may provide that the securities included in the unit may not be held or transferred separately at any time or at any time before a specified date. A copy of the forms of the unit agreement and the unit certificate relating to any particular issue of units will be filed with the SEC each time we issue units, and you should read those documents for provisions that may be important to you. For more information on how you can obtain copies of the forms of the unit agreement and the related unit certificate, see "Where You Can Find More Information."

The prospectus supplement relating to any particular issuance of units will describe the terms of those units, including, to the extent applicable, the following:

- the designation and terms of the units and the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provision for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units; and
- whether the units will be issued in fully registered or global form.

PLAN OF DISTRIBUTION

We may sell the securities offered by this prospectus in any one or more of the following ways from time to time:

- to or through one or more underwriters, initial purchasers, brokers or dealers;
- through agents to investors or the public;
- in short or long transactions;
- through put or call option transactions relating to our common stock;
- directly to agents or other purchasers;
- in "at the market offerings" within the meaning of Rule 415(a)(4) of the Securities Act, to or through a market maker or into an existing trading market, on an exchange or otherwise;
- through a combination of any such methods of sale; or
- through any other method described in the applicable prospectus supplement.

The applicable prospectus supplement will set forth the terms of the offering and the method of distribution and will identify any firms acting as underwriters, initial purchasers, dealers or agents in connection with the offering, including:

- the terms of the offering;
- the names of any underwriters, dealers or agents;
- the name or names of any managing underwriter or underwriters;

- the purchase price of the securities and the proceeds to us from the sale;
- any over-allotment options under which the underwriters may purchase additional shares of common stock from us;
- any underwriting discounts, concessions, commissions or agency fees and other items constituting compensation to underwriters, dealers or agents;
- any delayed delivery arrangements;
- any public offering price;
- any discounts or concessions allowed or re-allowed or paid by underwriters or dealers to other dealers; or
- any securities exchange or market on which the common stock offered in the prospectus supplement may be listed.

If we use underwriters for a sale of securities, the underwriters will acquire the securities for their own account for resale to the public, either on a firm commitment basis or a best efforts basis. The underwriters may resell the securities in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. Underwriters may offer the securities to the public either through underwriting syndicates represented by one or more managing underwriters or directly by one or more firms acting as underwriters. If an underwriter or underwriters are used in the sale of securities hereunder, an underwriting agreement will be executed with the underwriter or underwriters at the time an agreement for sale is reached. Unless we inform you otherwise in the applicable prospectus supplement, the obligations of the underwriters to purchase the securities will be subject to certain conditions. We may change from time to time any public offering price and any discounts or concessions the underwriters allow or pay to dealers.

During and after an offering through underwriters, the underwriters may purchase and sell the securities in the open market. These transactions may include overallotment and stabilizing transactions and purchases to cover syndicate short positions created in connection with the offering. The underwriters may also impose a penalty bid, which means that selling concessions allowed to syndicate members or other broker-dealers for the offered securities sold for their account may be reclaimed by the syndicate if the offered securities are repurchased by the syndicate in stabilizing or covering transactions. These activities may stabilize, maintain or otherwise affect the market price of the offered securities, which may be higher than the price that might otherwise prevail in the open market. If commenced, the underwriters may discontinue these activities at any time.

Some or all of the securities that we offer through this prospectus may be new issues of securities with no established trading market. Any underwriters to whom we sell our securities for public offering and sale may make a market in those securities, but they will not be obligated to do so and they may discontinue any market making at any time without notice. Accordingly, we cannot assure you of the liquidity of, or continued trading markets for, any securities that we offer.

If dealers are used for the sale of securities, we, or an underwriter, will sell the securities to them as principals. The dealers may then resell those securities to the public at varying prices determined by the dealers at the time of resale. We will include in the applicable prospectus supplement the names of the dealers and the terms of the transaction.

We may also sell the securities through agents designated from time to time. In the applicable prospectus supplement, we will name any agent involved in the offer or sale of the offered securities, and we will describe any commissions payable to the agent. Unless we inform you otherwise in the applicable prospectus supplement, any agent will agree to use its reasonable best efforts to solicit purchases for the period of its appointment.

We may sell the securities directly in transactions not involving underwriters, dealers or agents.

We may sell the securities directly to institutional investors or others who may be deemed to be underwriters within the meaning of the Securities Act with respect to any sale of those securities. We will describe the terms of any such sales in the prospectus supplement.

Underwriters, dealers and agents that participate in the distribution of the securities may be underwriters as defined in the applicable securities laws and any discounts or commissions they receive from us and any profit on their resale of the securities may be treated as underwriting discounts and commissions under the applicable securities laws. We will identify in the applicable prospectus supplement any underwriters, dealers or agents and will describe their compensation. We may have agreements with the underwriters, dealers and agents to indemnify them against specified civil liabilities, including liabilities under the applicable securities laws.

Underwriters, dealers and agents may engage in transactions with or perform services for us in the ordinary course of their businesses for which they may receive customary fees and reimbursement of expenses.

We may use underwriters with whom we have a material relationship. We will describe the nature of such relationship in the applicable prospectus supplement.

Under the securities laws of some states, the securities offered by this prospectus may be sold in those states only through registered or licensed brokers or dealers.

We may enter into hedging transactions with broker-dealers and the broker-dealers may engage in short sales of the securities in the course of hedging the positions they assume with us, including, without limitation, in connection with distributions of the securities by those broker-dealers. We may enter into option or other transactions with broker-dealers that involve the delivery of the securities offered hereby to the broker-dealers, who may then resell or otherwise transfer those securities. We may also loan or pledge the securities offered hereby to a broker-dealer and the broker-dealer may sell the securities offered hereby so loaned or upon a default may sell or otherwise transfer the pledged securities offered hereby.

LEGAL MATTERS

The validity of the securities being offered hereby will be passed upon for us by Morgan, Lewis & Bockius LLP, New York, New York.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K/A for the year ended December 31, 2015, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and other reports, proxy and information statements and other information with the Securities and Exchange Commission. Copies of these materials may be inspected and copied at the public reference facilities maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of its public reference room. The SEC maintains a website that contains reports, proxy statements and other information regarding us. The address of the SEC website is www.sec.gov. We maintain a website at www.axsome.com. Information contained on our website is not incorporated into this prospectus and you should not consider information contained on our website to be part of this prospectus or any prospectus supplement.

INFORMATION INCORPORATED BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus the information contained in documents that we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC before the date of this prospectus, while information that we file later with the SEC will automatically update and supersede prior information. Any information so updated and superseded shall not be deemed, except as so updated and superseded, to constitute a part of this prospectus. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, prior to the termination of the offering. Notwithstanding the foregoing, unless specifically stated to the contrary, none of the information that is not deemed "filed" with the SEC, including information furnished under Items 2.02 or 7.01 of any Current Report on Form 8-K, will be incorporated by reference into, or otherwise included in, this prospectus:

1. our annual report on Form 10-K for the fiscal year ended December 31, 2015 filed with the SEC on March 24, 2016 (the "Form 10-K"), and amended on August 9, 2016;
2. the information contained in our definitive proxy statement on Schedule 14A for our 2016 annual meeting of stockholders filed with the SEC on April 27, 2016, to the extent incorporated by reference in Part III of the Form 10-K;
3. our quarterly report on Form 10-Q for the quarter ended March 31, 2016 filed with the SEC on May 11, 2016, and amended on August 9, 2016;
4. our quarterly report on Form 10-Q for the quarter ended June 30, 2016 filed with the SEC on August 9, 2016;
5. our quarterly report on Form 10-Q for the quarter ended September 30, 2016 filed with the SEC on November 14, 2016;
6. our current reports on Form 8-K filed with the SEC on March 22, 2016, March 29, 2016 (as to Item 8.01 and Exhibit 99.2 only), April 21, 2016, May 5, 2016, June 10, 2016, July 12, 2016, September 2, 2016 and November 10, 2016; and
7. our description of our common stock contained in the registration statement on Form 8-A, filed on November 16, 2015, and all amendments and reports updating such description.

We make available, free of charge, through our website 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 Section 13(a), 13(c), 14 or 15(d) of the Exchange Act as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. You may also obtain, free of charge, a copy of any of these documents (other than exhibits to these documents unless the exhibits are specifically incorporated by reference into these documents or referred to in this prospectus) by writing or calling us at the following address and telephone number:

Axsome Therapeutics, Inc.
25 Broadway
9th Floor
New York, New York 10004
(212) 332-3241

Shares

AXSOME

THERAPEUTICS

Common Stock

Prospectus Supplement
, 2017

Sole Book-running Manager

Ladenburg Thalmann
