October 13, 2015

VIA EDGAR AND FEDEX

Suzanne Hayes
Assistant Director
United States Securities and Exchange Commission
Division of Corporate Finance
100 F Street, N.E.
Washington, D.C. 20549

Re: Axsome Therapeutics, Inc.
Draft Registration Statement on Form S-1
Submitted August 25, 2015
CIK No. 0001579428

Dear Ms. Hayes:

On behalf of our client, Axsome Therapeutics, Inc. ("we" or the "Company"), set forth below is the Company's response to the letter dated September 22, 2015 (the "September 22 Comment Letter") from the staff (the "Staff") of the Securities and Exchange Commission (the "Commission"), which relates to the Company's Draft Registration Statement on Form S-1, CIK No. 0001579428 (the "Registration Statement") submitted to the Commission on August 25, 2015 (the "Initial Submission"). The Company is filing the Registration Statement (the "Revised Registration Statement"), which includes revisions made to the Initial Submission in response to the September 22 Comment Letter, and to reflect certain additional information. An electronic version of the Revised Registration Statement has been filed concurrently with the Commission through its EDGAR system. The enclosed copy of the Revised Registration Statement has been marked to reflect changes made to the Registration Statement.

The numbered paragraphs and headings below correspond to the headings set forth in the September 22 Comment Letter. Each of the Staff's comments is set forth in bold, followed by the Company's response to each comment. The page numbers in the bold captions refer to pages in the Initial Submission, while the page numbers in the Company's responses refer to page numbers in the Revised Registration Statement. Capitalized terms used in this letter but not defined herein have the meaning given to such terms in the Revised Registration Statement.

Prospectus Summary
Overview, page 1

1. Please describe the meaning and significance of the following terms the first time you use them in this section:

- **Osteoclast inhibitor;**
- **Zoledronic acid; and**
- **Bone resorption markers.**

Response:

In response to the Staff's comment, the Company has revised the following disclosures on page 1 of the Revised Registration Statement to now state:

"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."

"In this trial, 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."

Our Pipeline, page 3

2. On page 5, you state that you plan to request a meeting with the FDA in 2016 to discuss your development plans for AXS-05 for the treatment of agitation in patients with AD. Your table should clearly indicate which phases of clinical trials have been completed. As your discussion states that you have completed phase 1 clinical trials, please revise your pipeline table to remove the gray portion of the arrow.

Response:

In response to the Staff's comment, the Company has revised the pipeline table throughout the Revised Registration Statement to reflect the change requested above.

AXS-02, page 3

3. At your first reference to the 505(b)(2) regulatory development pathway, please expand your disclosure to describe this process and its significance to your

development of AXS-02 and AXS-05. Similarly, please provide the meaning and significance of FDA Fast Track designation the first time you refer to it on page 3.

Response:

In response to the Staff's comment, the Company has added the following disclosure to pages 1 and 3 of the Revised Registration Statement, respectively:

"Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, or FDCA, enables a potentially shorter development timeline for our product candidates by allowing us to rely, in part, upon published literature or the FDA's previous findings of safety and efficacy for an approved product with the active molecules in our product candidates and potentially forego conducting certain clinical trials and certain lengthy and costly preclinical studies."

"The FDA's Fast Track program is designed to expedite the development and review of drugs that are intended to treat serious or life-threatening conditions by providing greater access to, and more frequent communication with, the FDA throughout the drug development process."

Risk Factors, page 13

4. Under an appropriately titled risk factor, please discuss Dr. Tabuteau's conflicts of interest as your CEO and owner of Antecip. The discussions should address conflicts relating to the license agreements; his roles as your CEO and Chairman of the Board and managing member of Antecip; and the allocation of his time between these roles.

Response:

In response to the Staff's comment, the Company has inserted the following risk factor on page 17 of the Revised Registration Statement:

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

In 2012, we entered into three exclusive license agreements with Antecip Bioventures II LLC, or Antecip, an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which we were granted exclusive licenses to develop, manufacture, and commercialize Antecip's patents and applications related to the development of our current product candidates. See "Business—Material License Agreements." Although Dr. Tabuteau dedicates all of his working time to us because Antecip is an inactive intellectual property holding company, he may face potential

conflicts of interest regarding these licensing transactions as a result of his ownership of Antecip. The license agreements provide that, subject to the reasonable consent of Antecip, we have the right to control the prosecution or defense, as the case may require, of a patent infringement claim involving the licensed intellectual property. Our interests with respect to pleadings and settlements in such cases may be at odds with those of Antecip. If there is a dispute between us and Antecip, Dr. Tabuteau will have a conflict of interest because he may, at the time of a prospective dispute, simultaneously have a financial interest in and owe a fiduciary duty to Antecip and simultaneously have a financial interest in and owe a fiduciary duty to us. For example, if a contractual dispute arises between us and Antecip under any of the license agreements we have with Antecip, Dr. Tabuteau may be in a position where he would benefit if Antecip prevails, to the detriment of our business or our investors, even though he is an officer and director of our company, because he is the sole owner of Antecip. Similarly, if we have a claim of any kind against Antecip, Dr. Tabuteau may be, even as our Chief Executive Officer and Chairman of the Board, reluctant to assert a claim by us against Antecip because of his financial interest in Antecip. We cannot assure you that any conflicts will be resolved in our favor, and as a result, our business could be impeded or materially harmed."

Risks Related to Intellectual Property
Obtaining and maintaining our patent protection depends on compliance with…, page 47

5. The title of this risk factor references compliance with various procedural, documentary, fee payment, and other requirements imposed by governmental patent agencies in order to obtain and maintain your patent protection; however, your risk factor disclosure does not discuss any of these requirements and the risks associated with them. Please revise your risk factor disclosure to discuss the referenced requirements, which government agencies have imposed them and the risk of non-compliance with the requirements.

Response:

In response to the Staff's comment, the Company has revised the body of this risk factor on page 49 of the Revised Registration Statement to now state:

"The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment, and other similar provisions during the patent prosecution process. Periodic maintenance fees, renewal fees, annuity fees, and various other governmental fees on patents or patent applications will be due to be paid to the USPTO and various patent agencies outside of the United States in several stages over the lifetime of the patents and applications. We have systems in place to remind us to pay these fees, and we employ and rely on reputable law firms and other professionals to effect payment of these fees to the USPTO and non-U.S. patent agencies for the patents and patent applications we own and those that we in-license. We also employ reputable law firms and other professionals to help us comply with the various

documentary and other procedural requirements with respect to the patents and patent applications that we own and those that we in-license. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business."

We may be involved in lawsuits to protect or enforce our patents or the patents…, page 49

6. Please expand your risk factor disclosure to describe whether you or Anticep is responsible for enforcement of the patents you license from Anticep.

Response:

In response to the Staff's comment, the Company has revised the body of this risk factor on page 50 of the Revised Registration Statement:

"Competitors may infringe our issued patents, our in-licensed patents, or other intellectual property that we own or in-license. Under the terms of our license agreements with Antecip, if we believe a third party is infringing on the patents subject to the licenses, we are obligated, at our own expense, to initiate suit against those third parties. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part; construe the patent's claims narrowly; or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

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

Use of Proceeds, page 66

7. Please revise your disclosure in the first two bullet points to describe how far in the development process of AXS-02 and AXS-05 you estimate the allocated proceeds from this offering will enable you to reach for each of the listed indications.

Response:

In response to the Staff's comment, the Company has revised the bullet points on page 68 of the Revised Registration Statement to now state:

· "approximately $19 to $25 million to fund our clinical trials for AXS-02, including the completion of our ongoing Phase 3 trial in pain associated with CRPS and our planned Phase 3 trial in the pain of knee OA associated with BMLs, and the launch of our planned Phase 3 trial in CLBP associated with MCs;
· approximately $14 to $17 million to fund our ongoing development of AXS-05, including the launch and completion of our planned Phase 3 trial of AXS-05 in TRD; and
· the remainder for further development of our product candidates, working capital, and general corporate purposes."

Management's Discussion and Analysis of Financial Condition and Results of Operations
Critical Accounting Policies and Significant Judgments and Estimates
Stock-Based Compensation and Fair Market Value of Stock, page 73

8. We may have additional comments on your accounting for equity issuances including stock based compensation. Once you have an estimated offering price, please provide us an analysis explaining the reasons for the differences between the recent valuations of your common stock leading up to the IPO and the estimated offering price.

Response:

The Company acknowledges the Staff's comment and respectfully advises the Staff that the Company will provide the Staff with this analysis at such time as an estimated offering price has been determined.

Business
Overview, page 86

9. Please identify the one product that is approved in the United States for the treatment of TRD.

Response:

In response to the Staff's comment, the Company has revised the following sentence on page 89 of the Revised Registration Statement to now state:

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

AXS-02, page 89

10. Under the appropriate subsection for AXS-02, please disclose when an investigational new drug application ("IND") was filed for the commencement of clinical trials for the product candidate, the name of the trial sponsor and the subject of the IND.

Response:

In response to the Staff's comment, the Company has added the following disclosure to page 98 of the Revised Registration Statement:

"We submitted an Investigational New Drug Application, or IND, sponsored by us, in October 2013 for AXS-02 for the treatment of pain associated with CRPS."

Rationale for the Use of AXS-02 in CPRS
Effects of AXS-02 in the rat tibia fracture model of CRPS, page 92

11. We note your disclosure in the first full paragraph on page 93 that oral administration of AXS-02 "significantly" reversed pain, improved weight bearing and prevented edema as compared to placebo in the rat tibia fracture model of CRPS and the related p-values shown in the accompanying figure. Please revise your disclosure to clarify that the improvement in pain, weight bearing and edema was statistically significant. In addition, please explain the relationship between "statistical significance" and "p-values" and the significance of p-values to the FDA's evidentiary standards of efficacy.

Response:

In response to the Staff's comment, the Company has revised the first sentence of the first full paragraph on page 95 of the Revised Registration Statement to now state:

"Oral administration of AXS-02 resulted in a statistically significant reduction in pain, improvement in weight bearing, and prevention of edema as compared to placebo in the rat tibia fracture model of CRPS."

In addition, the Company has added the following sentences to the end of that same paragraph:

"An experimental result, such as those derived from a clinical or non-clinical study, is statistically significant if it is unlikely to have occurred by chance. The statistical significance of experimental results is determined by a widely used statistical method that establishes the P value of the results. A P value is a statistical measure of the probability that the difference in results between treatment and control groups in a study could have occurred by chance. Under this method, the smaller the P value the greater the confidence that the results are significant, and a P value of 0.05 or less is generally considered by the FDA to represent statistical significance."

12. Please expand your disclosure regarding the second study using the same rat tibia model where the results of the study showed a "significant" reduction in pain and "improvement" in weight bearing to provide the results of the trial which led to this conclusion. If the reduction in pain was also "statistically significant" in this study, please revise your disclosure to use the term "statistically significant" rather than the term "significant." Please also make similar revisions to your disclosure for the other clinical trials discussed in your prospectus to use the term "statistically significant" rather than "significant" where appropriate.

Response:

In response to the Staff's comment, the Company has revised the final paragraph on page 95 of the Revised Registration Statement to now state:

"We conducted a second study using the same rat tibia fracture model. In this study, the animals underwent tibia fracture and casting as described above, but dosing of AXS-02 was started following cast removal and continued for a duration of three weeks. Oral administration of AXS-02 resulted in a statistically significant reversal of pain and improvement in weight bearing as compared to placebo. Treatment with AXS-02 reversed pain by approximately 100% versus baseline and improved weight bearing by approximately 13% as compared to placebo. The study did not find an effect of AXS-02 on edema or hindpaw temperature."

Further, in response to the Staff's comment, the Company has made several revisions throughout the Revised Registration Statement to use the term "statistically significant" where appropriate.

AXS-05
Overview, page 101

13. Please revise your diagram on page 102 to define the acronym DXO.

Response:

In response to the Staff's comment, the Company has revised the diagram on page 104 of the Revised Registration Statement to define the acronym DXO. In addition, the Company has inserted the following additional disclosure on page 104 of the Revised Registration Statement:

"DM is active at multiple CNS receptors but is rapidly metabolized into dextrorphan, or DXO, when dosed alone."

Treatment Resistant Depression
Rationale for the Development of AXS-05 in Agitation in Patients with AD, page 105

14. We note that a significantly greater reduction for active treatment as compared to placebo in the agitation/aggression domain of the NPI was seen in both stage 1 and stage 2 of the study discussed in this section. Please expand your disclosure to also provide the results of stage 2 of the study which support this conclusion.

Response:

In response to the Staff's comment, the Company has revised the second sentence in the second full paragraph on page 108 of the Revised Registration Statement to now state:

"A statistically significantly greater reduction in the agitation/aggression domain of the NPI for active treatment as compared to placebo was seen in both stage 1 as well as in stage 2 of the study. During stage 1, a reduction of 3.3 in the agitation/aggression domain of the NPI was seen for active treatment as compared to a reduction of 1.7 for placebo, with a P value that is less than 0.001, as shown in the figure below. During stage 2, a reduction of 2.0 was observed for active treatment as compared to a reduction of 0.8 for placebo, with a P value that is equal to 0.02. Average baseline values for the agitation/aggression domain of the NPI were 7.1 for the active treatment group and 7.0 for the placebo group."

Preclinical Programs, page 108

15. We note your disclosure on pages 17 and 108 that AXS-04 is a product candidate that is currently in early-stage development. If this product candidate is in preclinical development, please expand your disclosure in this section and throughout your prospectus as appropriate to describe AXS-04. Otherwise, please advise us supplementally if you have not yet identified an indication for this product candidate and have therefore concluded that it is premature to include it in your preclinical program discussion.

Response:

In response to the Staff's comment, the Company confirms that it has not yet identified an indication for AXS-04 and the Company has therefore concluded that it would be premature to include further information in the preclinical program discussion.

Intellectual Property, page 109

16. Please revise your disclosure for your patent portfolio for AXS-02 and AXS-05 to provide the following information:

- **whether the patents are owned or licensed from Anticep;**
- **the expiration date of issued patents separate from the expected expiration dates if your patent applications are approved;**
- **the foreign jurisdictions where your AXS-02 patents are issued and patent applications are pending; and**
- **the jurisdictions where your AXS-05 patent is issued and patent applications are pending.**

Response:

In response to the Staff's comment, the Company has revised the first full paragraph on page 112 of the Revised Registration Statement to now state:

"Our intellectual property portfolio contains 13 issued patents and 3 allowed and more than 50 pending applications in the United States and worldwide. Twelve issued patents and more than 35 pending patent applications covering our AXS-02 product candidate have claims covering method of delivery, pharmacokinetics, composition of matter, and methods of use with protection extending through 2034 for both our issued patents and pending applications. In addition to patent protections, our AXS-02 program, if approved, may also be afforded potential exclusivity by the FDA's and EMA's orphan drug designation programs for CRPS, which provide 7 years and 10 to 12 years of exclusivity, respectively. One issued patent and 3 allowed and several pending patent applications covering our AXS-05 product candidate have claims covering pharmaceutical composition, drug delivery, and pharmacokinetics with protection extending through 2032 to 2034 for our issued and allowed patents, as well as our pending applications. We have pending PCT applications, as well as pending applications in Australia, Canada, China, Europe, Hong Kong, Japan, South Korea, and New Zealand. We have other patent applications with claims covering the other programs in our pipeline, including those that are not relevant to our current programs in development. We have licensed the patents and pending applications which cover AXS-02, AXS-04, and AXS-05 from Antecip. All of the other components of our intellectual property portfolio are owned by Axsome."

Certain Relationships and Related Party Transactions
Consulting Agreement with Mark Coleman, M.D.

17. Please file the consulting agreement with Mr. Coleman as an exhibit.

Response:

The Company acknowledges the Staff's comment and respectfully advises the Staff that Dr. Coleman's consulting agreement with the Company has been filed as an exhibit with the attached Revised Registration Statement.

Other Comments

18. We note that there are a number of additional exhibits that still need to be filed. Please provide these exhibits as promptly as possible. Please note that we may have comments on these materials once they are provided.

Response:

The Company acknowledges the Staff's comment and respectfully advises the Staff that most of the exhibits not filed with the Initial Submission are being filed with the attached Revised Registration Statement. The Company will provide the remaining exhibits as promptly as possible.

19. Please confirm that the graphics included in your registration statement are the only graphics you will use in your prospectus. If those are not the only graphics, please provide any additional graphics prior to their use for our review.

Response:

The Company acknowledges the Staff's comment and respectfully advises the Staff that the images included in the Registration Statement are all of the graphic, visual or photographic information the Company currently intends to include in the Registration Statement. If the Company decides to use any additional images, it will provide the Staff with proofs of such materials as soon as practicable.

20. Please supplementally provide us with copies of all written communications, as defined in Rule 405 under the Securities Act, that you, or anyone authorized to do so on your behalf, present to potential investors in reliance on Section 5(d) of the Securities Act, whether or not they retain copies of the communications.

Response:

The Company acknowledges the Staff's request and respectfully advises the Staff that, to date, no written communications, as defined in Rule 405 under the Securities Act, have

been presented by the Company, or anyone authorized to act on the Company's behalf, to potential investors. The Company intends to supplementally provide the Staff with copies of all such written communications presented to potential investors in reliance on Section 5(d) of the Securities Act as promptly as practicable following such presentation, if any. The Company advises the Staff that potential investors will not be permitted to retain copies of such written communications. The Company further advises the Staff that to its knowledge, as of the date hereof, no research reports have been distributed by any broker or dealer participating in the offering.

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Please contact the undersigned at (609) 919-6633 if you have any questions regarding the foregoing.

Sincerely,

/s/ Emilio Ragosa
Emilio Ragosa

cc: Herriot Tabuteau, Axsome Therapeutics, Inc.
Brian B. Margolis, Orrick, Herrington & Sutcliffe LLP