UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

EVY GRU, Individually and on Behalf of All Others Similarly Situated, Plaintiff, v. AXSOME THERAPEUTICS, INC., HERRIOT TABUTEAU, NICK PIZZIE, MARK JACOBSON, CEDRIC O'GORMAN, and KEVIN LALIBERTE, Defendants.	Case No.: 1:22-cv-3925-LGS **SECOND AMENDED CLASS ACTION COMPLAINT** **JURY TRIAL DEMANDED**

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Representative Plaintiffs _____ ("Plaintiffs"), individually and on behalf of all others similarly situated, by Plaintiffs' undersigned attorneys, alleges the following based upon personal knowledge as to Plaintiffs and Plaintiffs' own acts, and information and belief as to all other matters, based upon, *inter alia*, the investigation conducted by and through Plaintiffs' attorneys, which included, among other things, a review of the Defendants' (defined below) public documents, conference calls and announcements made by Defendants, United States ("U.S.") Securities and Exchange Commission ("SEC") filings, wire and press releases published by and regarding Axsome Therapeutics, Inc. ("Axsome" or "Company"), analysts' reports and advisories about the Company, interviews of confidential witnesses, and information readily obtainable on the Internet. Plaintiffs believe that substantial, additional evidentiary support will exist for the allegations set forth herein after a reasonable opportunity for discovery.[1]

I. INTRODUCTION

1. This is a federal securities class action on behalf of a class consisting of all persons and entities other than Defendants that purchased or otherwise acquired Axsome common stock between May 10, 2021, and April 22, 2022, both dates inclusive ("Class Period"), seeking to recover damages caused by Defendants' violations of Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 ("Exchange Act").

2. On April 25, 2022, Axsome, a New York-based biopharmaceutical company that develops novel therapies for central nervous system ("CNS") disorders, disclosed that due to chemistry, manufacturing, and controls ("CMC") issues, the United States Food & Drug Administration ("FDA") would reject its new drug application ("NDA" or "Application") for AXS-07—a product candidate for the acute treatment of migraine. The Company stated that the

[1] Emphases herein are added unless noted otherwise below.

FDA had identified CMC issues during its review of the Application. Defendants disclosed too that they expected the FDA to issue a Complete Response Letter ("CRL" or "Response")[2] "with respect to this NDA on or about the Prescription Drug User Fee Act target action date of April 30, 2022."[3] At the very least, these developments substantially delayed approval while Axsome addressed the CMC issues the FDA identified and resubmitted the AXS-07 NDA. In response to this news, Axsome's stock price plummeted approximately 22%.

3. AXS-07 is one of Axsome's five products from its core CNS portfolio, and, at the time, its closest to commercialization. In its Form 10-K for the year ending December 31, 2020 ("2020 10-K"), about AXS-07, the Company stated that it had completed two Phase 3 clinical trials for AXS-07 and another open-label trial. As of March, 2021, the Company stated, it "plan[ned] to submit an NDA for AXS-07 for the acute treatment of migraine." From no later than the end of the first quarter of 2021, Defendants knew or recklessly disregarded that CMC issues plagued the Company's development of AXS-07. Part of an NDA includes a section on the drug's chemistry, manufacturing, and controls. These CMC issues are an essential part of the drug development process. They ensure that the manufacturing process for the drug produces a product that is consistent with the specifications that were used in a more limited capacity during clinical trials.

4. For example, according to senior clinical trial personnel, one fatal CMC issue was that a contract manufacturing organization—a third party with whom Axsome contracted to produce AXS-07—had equipment problems throughout 2021 and leading up to the FDA review

[2] In a CRL the FDA informs the applicant that it is declining to approve an NDA. The FDA sends a CRL after it has completed the review of the NDA. A CRL is therefore a definitive statement that the NDA was not sufficient to support approval of the drug under consideration

[3] A target action date is the date under the Prescription Drug User Fee Act by which the FDA plans to review an NDA.

deadline in 2022. Accordingly, Axsome was simply unable to manufacture the drug for an extended duration during this crucial period of time during the FDA's review of its Application for AXS-07.

5. Indeed, Defendants knew that the necessary supply of AXS-07 for a clinical trial that Axsome had planned was unavailable, causing Axsome to delay the trial multiple times. Even in early 2022, the manufacturer remained unable to resolve its equipment problems. Given that the supply disruption delayed this trial—and manufacturing partners therefore could not produce AXS-07 even in limited supplies for trials—Defendants recklessly disregarded the CMC issues, ultimately causing the FDA to issue the CRL. Axsome's complete inability to manufacture AXS-07 was a severe manufacturing problem relevant to the "chemistry, ***manufacturing***, and controls" portion of the AXS-07 Application.

6. Also, according to clinical trial personnel, Defendants prioritized profit over patients, cutting corners during the drug development process, motivated to meet milestones they knew or recklessly disregarded had failed to meet. Indeed, the CMC issues with Axsome's AXS-07 NDA were the Company's second NDA in short succession for which the FDA found CMC issues. The Company also experienced CMC problems when it was attempting to submit an NDA for another one of its five core CNS products, AXS-05. Those issues also caused delays and put Defendants on notice of CMC issues with its NDAs.

7. Even as Defendants knew of or recklessly disregarded the AXS-07 CMC issues, they misrepresented them to investors. ***First***, Defendants affirmatively discussed CMC issues as supporting the AXS-07 NDA and did not mention the ongoing manufacturing problems with AXS-07. Defendants even repeated a continued refrain in Axsome's SEC filings throughout the

Class Period that the Company's suppliers would be capable of providing sufficient quantities of their product when the Company's supplier for AXS-07 was failing to do so.

8. ***Second***, Axsome promoted an unrealistic timeline for the submission of an NDA for AXS-07. Defendants constantly represented to investors that the NDA for AXS-07 would be filed in 2020, despite knowing of the significant CMC problems in the development process. Rather than submit the NDA for AXS-07 by the end of 2020, as Defendants had repeatedly promised, Axsome did not submit the NDA until June 2021.

9. ***Third***, throughout the Class Period, Defendants promoted the outcomes of AXS-07's clinical trials and Axsome's supposedly positive discussions with the FDA about those results as supporting the timely approval of its AXS-07 NDA. It was materially misleading for Defendants to promote the likely approval of AXS-07 based on these factors while omitting the material CMC problems that plagued the development of AXS-07—to the point where Axsome could not even manufacture the drug while its Application was under review.

10. These materially false and misleading statements harmed Axsome's investors. The Company's stock price sank when Axsome revealed the truth about the CMC problems with AXS-07—including falling 22% on April 25, 2022, after the Company revealed the FDA's concerns that caused it to deny the AXS-07 NDA.

II. JURISDICTION AND VENUE

11. The claims asserted herein arise under and pursuant to Sections 10(b) and 20(a) of the Exchange Act (15 U.S.C. §§ 78j(b) and 78t(a)) and Rule 10b-5 promulgated thereunder by the SEC (17 C.F.R. § 240.10b-5).

12. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. § 1331 and Section 27 of the Exchange Act.

13. Venue is proper in this Judicial District pursuant to Section 27 of the Exchange Act (15 U.S.C. § 78aa) and 28 U.S.C. § 1391(b). Axsome is headquartered in this Judicial District, Defendants conduct business in this Judicial District, and a significant portion of Defendants' activities took place within this Judicial District.

14. In connection with the acts alleged in this complaint, Defendants, directly or indirectly, used the means and instrumentalities of interstate commerce, including, but not limited to, the mails, interstate telephone communications, and the facilities of the national securities markets.

III. PARTIES

15. Plaintiff ___, as set forth in the Certification appended hereto, acquired the Company's common stock at artificially inflated prices during the Class Period and was damaged upon the revelation of the truth described below. Plaintiff _____, as set forth in the Certification appended hereto, acquired the Company's common stock at artificially inflated prices during the Class Period and was damaged upon the revelation of the truth described below.

16. Defendant Axsome is a Delaware corporation with principal executive offices located at 22 Cortlandt Street, 16th Floor, New York, New York 10007. Axsome's common stock trades in an efficient market on the NASDAQ under the trading symbol "AXSM". As of March 6, 2020, Axsome had 45 full-time employees. As of February 22, 2021, Axsome had 60 full-time employees. As on February 22, 2022, Axsome had 108 full-time employees.

17. Defendant Herriot Tabuteau, M.D. ("Tabuteau") founded Axsome in 2012 and has served as its Chief Executive Officer and Chairman of the Board of Directors since that time.

18. Defendant Mark Jacobson ("Jacobson") has served as Axsome's Chief Operating Officer since March 2020. Before then, he served as the Company's Senior Vice President of Operations since September 2017 and has been employed at the Company since April 2014.

19. Defendant Kevin Laliberte ("Laliberte") served as Axsome's Executive Vice President of Product Strategy from January 2021 to December 2021.

20. Defendant Nick Pizzie ("Pizzie") has served as Axsome's Chief Financial Officer since May 2018.

21. Defendant Cedric O'Gorman ("O'Gorman") served as Axsome's Senior Vice President of Clinical Development and Medical Affairs from September 2017 to September 2021.

22. Defendants Tabuteau, Jacobson, Laliberte, Pizzie, and O'Gorman are sometimes referred to herein as the "Individual Defendants." The Individual Defendants possessed the power and authority to control the contents of Axsome's SEC filings, press releases, and other market communications. The Individual Defendants were provided with copies of Axsome's SEC filings and press releases alleged herein to be misleading prior to or shortly after their issuance and had the ability and opportunity to prevent their issuance or to cause them to be corrected. Because of their positions with Axsome, and their access to material information available to them but not to the public, the Individual Defendants knew that the adverse facts specified herein had not been disclosed to and were being concealed from the public, and that the positive representations being made were then materially false and misleading. The Individual Defendants are liable for the false statements and omissions pleaded herein.

23. Axsome and the Individual Defendants are collectively referred to herein as "Defendants."

IV. SUBSTANTIVE ALLEGATIONS

A. Background

24. Axsome is a biopharmaceutical company based in New York City engaging in the development of novel therapies for CNS conditions that have limited treatment options.

25. Defendant Tabuteau founded Axsome in January 2012. The Company went public through an initial public offering on the NASDAQ stock exchange on November 19, 2015.

26. Two of Axsome's five core products from its CNS portfolio are its AXS-07 and AXS-05 treatments.

27. AXS-07 is a novel, oral, rapidly absorbed, multi-mechanistic, and investigational medicine for the acute treatment of migraine. Axsome described AXS-07 as part of its "core CNS portfolio." AXS-05 is a treatment of major depressive disorder ("MDD").

28. AXS-05 and AXS-07 are the first two products for which Axsome submitted NDAs to the FDA. They were, therefore, the closest to commercialization of the Company's drugs in development.

29. Axsome sought FDA approval for AXS-07 and AXS-05 under the FDA's 505(b)(2) regulatory development pathway. Under that pathway, companies submit an NDA "that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference."

30. Market analysts consistently rated the Company positively based on the value that AXS-07 was expected to add to the Company according to the optimistic safety and efficacy clinical trial results that Axsome reported for AXS-07 before the Class Period. For example, on December 30, 2019, a SunTrust Robinson Humphrey analyst, noting positive momentum, reported, "we think AXS-07 is approvable based on data reported this morning." The primary two

factors contributing to the SunTrust's $100 price target for Axsome stock were the commercialization of AXS-05 and AXS-07. Cantor Fitzgerald similarly published a December 30, 2019, report in which it raised its 12-month price target for Axsome from $104 per share to $125 per share based on the positive trial data for AXS-07.

31. Even as Axsome researched and developed therapies, it explained in its Annual Reports prior to the Class Period that it did "not currently own or operate any manufacturing facilities for the clinical or commercial production of our drug candidates." Instead, it used "independent contract manufacturing organizations, or CMOs," to manufacture its drugs and perform its clinical trials. Axsome explained that it "conduct[ed] periodic quality audits of" CMO's facilities, concluding that Axsome's CMOs "***will be capable of providing sufficient quantities***" of product "***to meet our clinical trial supply needs***."

B. AXS-07

32. Prior to and during the Class Period, Defendants consistently told investors that Axsome's Application for AXS-07 was proceeding smoothly along a rapid timeline. Defendants promoted positive test results and feedback from the FDA that they represented as supporting the AXS-07 Application. Axsome, however, delayed its submission of the NDA multiple times. Then, after submitting the NDA, Axsome announced that the FDA found CMC problems with the Application. This negative feedback, at the very least, would lead to substantial delays in Axsome being able to resubmit an NDA for AXS-07. As described below, since before the Class Period, Defendants knew of or recklessly disregarded the CMC problems that existed for AXS-07.

33. Axsome describes AXS-07 as "a novel, oral, rapidly absorbed, multi-mechanistic, investigational medicine under development for the acute treatment of migraine." AXS-07 consists of what the Company calls "MoSEIC™, or Molecular Solubility Enhanced Inclusion Complex," including meloxicam and rizatriptan. Axsome describes this as a "combination drug," which is "a

single drug product that consists of two or more active ingredients, with each component making a contribution to the claimed effect of the drug."

34. "Meloxicam is a long-acting nonsteroidal anti-inflammatory drug, or NSAID" with "potent pain-relieving effects." AXS-07 uses Axsome's proprietary MoSEIC™ technology to "substantially increase" the speed at which meloxicam takes effect "while potentially maintaining durability of action."[4] Rizatriptan is included in AXS-07 because it "may reduce the release of inflammatory mediators from trigeminal nerves" and "is approved as a single agent for the acute treatment of migraine."

35. In February 2019, Axsome reached an agreement with the FDA for the Company's planned MOMENTUM (Maximizing Outcomes in Treating Acute Migraine) Phase 3 trial of AXS-07. The Company represented that the FDA agreed that the protocol for the MOMENTUM trial (e.g., entry criteria, dose selection, endpoints) "adequately address objectives that, if met, will support filing of an NDA of AXS-07 for the indication of acute treatment of migraine in adults with or without aura."

36. A Phase 3 clinical trial is the final stage of study before a new drug is submitted to the FDA for approval through an NDA. Phase 1 typically involves a very small number of participants (usually 100 or fewer) and tests a drug's overall safety and dosage. Phase 2 typically tests the drug on a larger group of people (up to a few hundred) to assess its efficacy and further

[4] Axsome also explains that "AXS-07 consists of MoSEIC™, or Molecular Solubility Enhanced Inclusion Complex, meloxicam and rizatriptan. Meloxicam is a long-acting nonsteroidal anti-inflammatory drug, or NSAID, with COX-2, an enzyme involved in inflammation and pain pathways, preferential inhibition and potent pain-relieving effects. However, standard meloxicam has an extended time to maximum plasma concentration, or Tmax, which delays its onset of action. AXS-07 utilizes our proprietary MoSEIC™ technology to substantially increase the solubility and speed the absorption of meloxicam while potentially maintaining durability of action. Meloxicam is a new molecular entity for migraine enabled by our MoSEIC™ technology."

assess its safety. A drug that passes Phase 1 and Phase 2 can then be subject to Phase 3 trials. Phase 3 trials are the most rigorous, as they typically test the drug on a larger group of people in a more controlled manner, and possibly for longer duration, to further assess the drug's efficacy in comparison to current treatment options and safety.

37. Axsome initiated the MOMENTUM study in March 2019. On December 30, 2019, Axsome announced that AXS-07 had met its two regulatory co-primary endpoints in the MOMENTUM study. In particular, Axsome announced that it "achieved co-primary and key secondary endpoints and significantly improved migraine pain, freedom from most bothersome symptoms, and sustained pain freedom, in the MOMENTUM study." That is, by late 2019, Defendants knew that Axsome had shown efficacy and safety endpoints, supporting an NDA.

38. Indeed, the Company told investors that the results from the MOMENTUM study supported the filing of an NDA for AXS-07 for "the acute treatment of migraine." Moreover, "[b]ased on FDA feedback," the Company disclosed, "Axsome believes that MOMENTUM will be the only efficacy trial required to support an NDA filing for AXS-07 for the acute treatment of migraine" and that "Axsome plans to file the NDA in the second half of 2020."

39. Defendant Tabuteau stated in Axsome's December 30, 2019, press release that "[w]ith these positive [Phase 3] results, we look forward to filing an NDA for AXS-07 in the acute treatment of migraine in 2020."

40. Before the Class Period, Defendants disclosed that AXS-07 was proceeding along this timeline and would be a major milestone in the Company reaching the commercial stage of its key products.

41. Axsome also conducted a second Phase 3 trial on AXS-07 called INTERCEPT. The Company told investors this study would bolster the strength of its NDA even further. The Company initiated the INTERCEPT study in October 2019.

42. In April 2020, Axsome announced that AXS-07 achieved the co-primary endpoints in the INTERCEPT study. Axsome then proceeded to promote both the MOMENTUM and INTERCEPT studies as supporting the Company's NDA for AXS-07. That is, by early 2020, Defendants knew that Axsome had shown efficacy and safety endpoints in two Phase 3 clinical studies, further supporting an NDA.

43. In addition to what Axsome described as its positive results from MOMENTUM and INTERCEPT, the Company conducted a third "Phase 3, open-label, long-term safety extension study of AXS-07 . . . to further support the NDA filing," as the Company explained in a May 8, 2020, press release. The Company called this the MOVEMENT (Multimechanistic Treatment Overtime of Migraine Symptoms) trial, stating that it would support the planned NDA for AXS-07.

44. In August 2020, Axsome announced a successful Pre-NDA meeting with the FDA for AXS-07 for the acute treatment of migraine.

45. On August 10, 2020, Axsome stated in connection with its results for the second quarter of 2020, that "***we remain on track to submit the NDA for AXS-07 for the acute treatment of migraine in the fourth quarter***. To that end," the Company continued, "we have completed enrollment in the Phase 3 open-label safety extension trial of AXS-07 in migraine, which we call the MOVEMENT study to support the planned NDA filing. As we move towards the filing of our NDA[] in the fourth quarter . . . for AXS-07," the Company concluded, "our commercial team is focused on launch-readiness activities to ensure successful commercial execution."

46. Despite consistently assuring investors that AXS-07 was on track to have its NDA submitted in 2020 based on its successful results from its MOMENTUM, INTERCEPT, and MOVEMENT trials, Axsome surprised investors on November 5, 2020, announcing in its third quarter 2020 results that "Axsome now plans to submit the [AXS-07] NDA to the FDA in the first quarter of 2021, versus previous guidance of the fourth quarter of 2020, to allow for inclusion of supplemental manufacturing information to ensure a robust submission package." That is, having met primary endpoints for safety and efficacy in three Phase 3 clinical trials, Defendants blamed delay on the FDA's requiring information on manufacturing. Thus, with respect to CMC, by no later than November 2020, Defendants knew that manufacturing issues had delayed submission of the AXS-07 NDA from late 2020 into 2021. Having met efficacy and safety endpoints, Defendants manifest their knowledge and focus on manufacturing issues as an obstacle to filing the AXS-07 NDA.

47. Axsome's 2020 10-K, noted the Company's focus on CMC issues as an integral part of the FDA approval process. "Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product candidate as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements," the Company stated. It continued that "[t]he manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality, potency, and purity of the final product. Additionally," the Company stated, "appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life."

48. At this point, however, Axsome portrayed this issue arising from information related to the manufacturing of AXS-07 as a minor delay. Indeed, Axsome stated on November 5, 2020, that it could solve that manufacturing issue it disclosed simply by submitting more information to the FDA. Defendants assured that the "inclusion of supplemental manufacturing information," would address any FDA concerns and "ensure a robust submission package."

49. Axsome did not end up submitting its NDA for AXS-07 until June 2021—months after its already-delayed timeline of the first quarter of 2021 that the Company announced on November 5, 2020.

50. On September 14, 2021, Axsome announced that the FDA had "accepted for filing the Company's New Drug Application (NDA) for AXS-07 for the acute treatment of migraine, and has set a Prescription Drug User Fee Act (PDUFA) target action date of April 30, 2022 for the NDA."[5]

51. Defendant Tabuteau stated in the September 14, 2021, press release that "[t]he FDA's acceptance of the NDA for AXS-07 is an important milestone for Axsome as it brings us closer to potentially making this multi-mechanistic treatment available to migraine patients in need." Defendants added that "[w]e look forward to continued interactions with the FDA during the review process" and that the NDA for AXS-07 "is supported by results from two Phase 3 randomized, double-blind, controlled trials of AXS-07 in the acute treatment of migraine, the MOMENTUM and INTERCEPT trials."

[5] The PDUFA requires that companies pay a fee when they submit NDAs in order to enable the FDA to timely review NDAs. The standard timeline for the FDA to complete a review under the PDUFA is 10 months and is 6 months for priority reviews.

1. The FDA's Negative Feedback Regarding AXS-07

52. On April 25, 2022, before the market opened, Axsome announced that on April 22, 2022, the FDA informed the Company "that chemistry, manufacturing, and controls ('CMC') issues identified during the FDA's review of the Company's New Drug Application ('NDA') for its AXS-07 . . . are unresolved. Based upon the time remaining in the NDA review cycle, the Company expects to receive a Complete Response Letter ["CRL"] with respect to this NDA on or about the Prescription Drug User Fee Act target action date of April 30, 2022."

53. On this news, Axsome's stock price fell $8.60 per share, or 21.99%, on April 25, 2022, to close at $30.50 per share.

54. On April 25, 2022, William Blair published a report, describing this news as "obviously disappointing," noting that the stock is down 24% premarket and that this would cause a substantial delay in the approval of AXS-07.

55. Axsome's April 25, 2022, announcement that the FDA found CMC issues with AXS-07 indicates that the FDA had previously communicated its concerns to the Company. The announcement notes that the issues that the FDA had identified were "unresolved" as of April 22, 2022. In other words, since the June 2021 submission of the NDA, the FDA had conveyed the material CMC issues to Defendants and allowed Axsome a chance to resolve these issues. Rather than learning for the first time about these CMC issues, the Company had failed to address them. If the FDA had not told Axsome about these problems previously, the FDA would have simply stated that it would be issuing a CRL because of issues that it identified with the NDA. Instead, the resolution period that the FDA referenced indicates that it had given Axsome a chance to resolve these issues, but the Company failed to address them. Despite the FDA previously informing Axsome about these issues with the AXS-07 NDA, April 22, 2022, was the first time that Axsome publicly disclosed that the FDA had any concerns whatsoever with the AXS-07 NDA.

56. Moreover, regardless of whether the FDA had communicated these CMC issues to Axsome before April 22, 2022, they existed—and posed an extreme risk to the pending NDA—much earlier in the development process for AXS-07.

57. On May 2, 2022, Axsome announced that it received the Response from the FDA for the AXS-07 NDA. The Company stated that "[t]he CRL did not identify or raise any concerns about the clinical efficacy or safety data in the NDA, and the FDA did not request any new clinical trials to support the approval of AXS-07. The principal reasons given in the CRL relate to [CMC] considerations." The Company continued that "[t]he CRL identified the need for additional CMC data pertaining to the drug product and manufacturing process. Axsome believes that the issues raised in the CRL are addressable and intends to provide potential timing for a resubmission following consultation with the FDA." In other words, Axsome could not give any indication at that point in time as to when it might be able to resubmit an NDA for AXS-07.

2. Axsome's Development of AXS-07 was Plagued by CMC Issues

58. Part of an NDA includes completing a section on the drug's CMC. This relates to a company's process for manufacturing the product. It also confirms that the product that is being tested in a limited capacity in the approval process is consistent with the product that will be manufactured and sold commercially, in much larger quantities, following FDA approval. CMC requirements ensure that the manufacturing process produces a safe and effective drug that is consistent with the drug that was used in clinical trials and is the subject of an NDA.

59. For example, a contract research organization (CRO) that provides testing and research support services in the pharmaceutical industry explains that "[a]fter clinical trials the scale up process must ensure that the larger batches of product are the same and meet the same

specifications as the drug tested in the clinical trials. After the manufacturing process is qualified, lot release and in process testing will continue to take place."[6]

60. CMC issues are a crucial part of the FDA approval process because even if a drug is safe and effective, in theory, it must also be so in the real world. A drug should not be sold to the public if its sponsor cannot manufacture it to scale identical to the product it tested.

61. Axsome's development of AXS-07 was plagued by CMC issues. After the FDA issued the CRL for the AXS-07 NDA, Defendant Tabuteau stated on the Company's May 2, 2022, earnings call for the first quarter of 2022 that "[t]he principal reason given in the CRL relate to chemistry, manufacturing and controls or CMC considerations. The CRL identified the need for additional CMC data pertaining to the drug product and manufacturing process. We believe that all the issues raised in the CRL are addressable." While Tabuteau continued to promote the efficacy and safety aspects of its clinical trials for AXS-07, he was not able to provide any update as to its submission of a new NDA other than to say that "[w]e intend to provide potential timing for a resubmission following consultation with the FDA."

62. Later, on this May 2, 2022, conference call, in a response to a request for more information about the CRL for AXS-07, Defendant Jacobson explained that "as we mentioned, the questions and the request for additional information, they principally relate to drug product and the manufacturing process. So just a reminder that AXS-07 incorporates our MoSEIC technology, with a novel technology that Axsome developed." He concluded, "[a]nd so that does increase the complexity of the manufacturing process, the MoSEIC technology. And so we understand the basis for many of the questions, and we do believe they're addressable." This indicates that Defendants knew before submitting the NDA of the complex manufacturing process for AXS-07.

[6] https://pacificbiolabs.com/cmc-chemistry-manufacturing-and-controls.

63. Tabuteau also noted, conciliatorily—now that the public was aware of CMC problems with AXS-07—that "we fully understand the reasons why the [FDA] would want to make sure that any new technology, any new manufacturing process is fully vetted."

64. The most that Tabuteau could say as to timing was that "[w]hat we're looking to do is to meet with the FDA as expeditiously as possible. That's a Type A meeting. We want to make sure that we get our ducks in a row prior to requesting that meeting and getting a date. Once we have that meeting and we get feedback from the agency. In other words, we confirm exactly what it is that should go into the resubmission that we can have success, then we'll be in a position to provide you with updated guidance on timing." He also noted "that we do expect that once we resubmit that the resubmission would likely be treated as a Class II resubmission, leading to a six-month review."

65. In addition, in response to a question about whether the CRL addressed any other issues beyond CMC questions, Tabuteau stated that it dealt "principally with all CMC" but "there was one item related to non-clinical, which was just our quest for additional information, which we believe we can provide. So for us, the real focus is this is a stand [stet] focus is CMC." In other words, the CRL also raised a non-CMC issue that Axsome did not fully describe.

66. While Defendants have been vague in their public disclosures as to the nature of the CMC problems that the FDA identified with AXS-07, Confidential Witness 1 ("CW 1") a former employee, who was a Senior Clinical Trial Manager at Axsome from July 2019 to February 2022, provided details of what the issues were.

67. CW 1 reported to the Executive Director of Clinical Research (Amanda Jones), the Director of Clinical Operations (Cheryl Askew), and the Senior Director of Clinical Operations

(Caroline Streicher) at various points during CW 1's tenure at the Company. CW 1 was based in Axsome's New York City office.

68. In early 2021, CW 1 was tasked to start managing a new study to provide additional data for AXS-07 that was scheduled to begin at the end of April 2021. The purpose of this study was to support the marketing of AXS-07 with additional published data. Manufacturing issues, however, forced the Company to delay that study first until August 2021 and then until November 2021. Axsome did not have a sufficient supply of AXS-07 for the study.

69. As the start of the study approached in early 2021, Axsome's available AXS-07 supply neared expiration. This forced the Company to arrange for production of more for the study. According to CW 1, around August 2021, Fang Liu, Axsome's Senior Director of Supply Chain for AXS-07, told CW 1 directly that one of the contract manufacturing organizations that Axsome contracted with to produce AXS-07 was having equipment problems and was therefore unable to manufacture the drug.

70. CW 1 recounts that Liu reported to Defendants Jacobson and Laliberte. In her role as the point person at Axsome regarding the supply of AXS-07, CW 1 recalls that Liu was aware of the manufacturing problems, dealt with supply delays of the drug due to the equipment issues, and provided updates to Jacobson and Laliberte about the status of drug supplies.

71. According to CW 1, in the summer of 2021, Axsome conducted an internal audit of its CMC operations and manufacturing facilities. CW 1 understood that the audit was done in preparation of the FDA's review as part of the NDA process for AXS-07 and AXS-05.

72. Also according to CW 1, equipment problems at the manufacturing facilities were raised in the audit. Defendant Laliberte was further aware of these problems as he was directly

involved in Axsome's response to the audit's results. CW 1 recalls an internal meeting where Laliberte affirmatively discussed Axsome's equipment issues that were raised in the internal audit.

73. As the months passed, Axsome continued to wait for the necessary supply of AXS-07. With AXS-07's continued unavailability, the Company delayed the study again, this time planning to conduct it in early 2022. At that point, Liu told CW 1 again that the manufacturer was ***still*** having equipment problems that it was not able to resolve. These problems therefore persisted at least from April 2021 through when CW 1 left the Company in February 2022.

74. According to CW 1, Axsome used one vendor to supply meloxicam and another vendor to supply rizatriptan, which are the two active ingredients in AXS-07. Axsome then used a third vendor to combine the two products to make AXS-07. It was this third vendor that could not produce AXS-07, having problems with the equipment used to combine the two molecules.

75. CW 1 recounts that the whole supply of AXS-07 for trial and commercial uses was manufactured at the same facility. CW 1 understood that the manufacturing delay due to the equipment problems delayed Axsome's entire supply of AXS-07, not just batches that were intended for use in trials. Liu told CW 1 that Axsome was waiting for the vendor to fix the equipment and was not trying to find a new vendor to manufacture the drug.

76. According to CW 1, the CMC issues that the FDA identified in its CRL for AXS-07 involved this contract manufacturing organization's equipment problem.

77. Further, according to CW 1, Axsome's executive management would have known about the CMO's equipment problems.

78. In addition executive management's knowledge or reckless disregard of CMO problems comports with the manufacturing problems as CW 1 understood them. CW 1 observed that the Company was not able to produce one of its core drug candidates, which was one of only

two drugs for which the Company was in the process of submitting NDAs. This delay went on for an extended period of time and caused a trial that Axsome was working on to be delayed indefinitely. Axsome's senior management would have known of this delay that made the Company completely unable to manufacture, or conduct studies on, one of its main products for an extended period of time.

79. Moreover, the timing of this delay in Axsome's ability to manufacture AXS-07 coincided with the FDA's review of the NDA for the drug. Axsome delayed the submission of the NDA from the end of 2020 to the first quarter of 2021, and then delayed it again, to the second quarter of 2021. This timing aligns with the delay in the ability of Axsome's CMO to manufacture AXS-07 for a study that was initially scheduled to begin in April 2021, but then ended up being delayed indefinitely over the course of the FDA's review of the Application. The timing also coincides with Axsome's audit of the manufacturing facilities which confirmed equipment issues.

80. Manifesting Defendants' actual knowledge of and focus on the CMO problem that caused the FDA ultimately to reject the AXS-07 NDA and to issue the CRL, on the Company's March 1, 2021, earnings call for the fourth quarter of 2020, an analyst asked why the AXS-07 NDA submission had been pushed back to the second quarter of 2021. Defendant Tabuteau responded that "[w]ith regard [AXS-]07 and the NDA filing the team remains on track to complete the filing by the end of the quarter. However, we are waiting on one vendor report which will slip into very beginning of the second quarter and that's the reason[.]" While Tabuteau did not disclose any information about the vendor's actual problems with manufacturing AXS-07 or indicate that such problems existed, his statement about the timing of the vendor's report corroborates CW 1's description of when the vendor's manufacturing problems arose. In the context of having shown

safety and efficacy of AXS-07 through two Phase 3 clinical trials, Defendant Tabuteau's response also indicates that he was focused with precision on the issues delaying the NDA.

81. This manufacturing problem with AXS-07 was particularly material because the CMO's inability to manufacture enough of the drug even for limited clinical trials demonstrates Axsome's inability to produce AXS-07 on the timeline and scale necessary for commercializing it. Indeed, CW 1 confirmed that the manufacturing delay halted Axsome's entire ability to produce AXS-07 for all purposes. Defendant Tabuteau also confirmed that Axsome produced its trial and commercial batches of AXS-07 at the same manufacturer.

82. Moreover, the manufacturing problem with AXS-07 stemmed from the particularly complex nature of the drug, requiring a third vendor focused specifically on combining the component parts of AXS-07 that were themselves obtained from two separate vendors.

83. All of these factors show that Axsome's extended problems with manufacturing AXS-07 were not just run-of-the mill equipment problems, but rather, were material obstacles, preventing the Company from successfully manufacturing AXS-07 for commercial purposes.

84. Defendants' disclosure of the delay in submitting the AXS-07 Application, followed by the CRL, confirms, in material part, the information from CW 1. For example, Axsome announced on November 5, 2020, that it was delaying its submission of its NDA for AXS-07 "to allow for inclusion of supplemental manufacturing information to ensure a robust submission package." On the Company's November 5, 2020, earnings call, an analyst asked Defendants to "provide more specifics on what manufacturing data related to the MoSEIC platform will be added for AXS-07." Defendant Tabuteau gave the following response:

> Great. So with regards to the additional manufacturing information, this is a standard information when you manufacture additional batches. So we continue to manufacture additional batches of drugs. And while we already have very long-term stability data on other batches, we think that because of the unique nature

> of the delivery technology, this can only help to make the submission robust and assure that there are no hiccups during review.

85. Tabuteau's explanation indicates that the Company continued to focus on the "long-term stability" of the manufacturing capacity it needed to commercialize AXS-07, with knowledge of the complexity of the manufacturing issue that confronted it with respect to AXS-07. Tabuteau's responses also demonstrate that the problem that CW 1 observed with Axsome's CMO for AXS-07 being able to manufacture the product is consistent with the topics that Tabuteau discussed.

86. In addition, as noted above, Defendants disclosed on May 2, 2022, that the CRL related "to the drug product and manufacturing process."

87. As Berenberg Capital Markets explained in an April 25, 2022, report, the CMC problems with AXS-07 "may be due to inadequacies with the manufacturing process," such as "the facility's manufacturing process" or "quality control of the drug," including "consistency of the drug product," "inconsistency between drug bunches," or "supply shortages, resulting in the company's inability to find a replacement for the material in need."[7] These types of problems are precisely what CW 1 observed.

88. In addition to the specific issue related to the manufacturing of AXS-07, CW 1's observations reflect a more systemic problem with Axsome's quality controls. CW 1 commented

[7] The full language from the Berenberg report stated that the CMC problems with AXS-07 "may be due to inadequacies with the manufacturing process, either related to 1) the facility's manufacturing process; or 2) quality control of the drug. Facility-related issues include missing documentation, lack of material/in-process controls, or required modifications to existing protocol (typically a significantly long process). Potential drug quality issues tie to consistency of the drug product and its safety and stability, including impurities in the product, inconsistency between drug bunches, or inadequate stability of the product (may take up to 24 months to prove). An additional potential CMC issue could be supply shortages, resulting in the company's inability to find a replacement for the material in need."

that the Company's executive leadership appeared to prioritize profit over patients and that they "cut corners." In addition, the Company seemed to always be in a rush to meet milestones.

89. For example, another CMC issue that beleaguered the AXS-07 NDA involved testing for the product's stability. On September 29, 2022, Axsome issued a press release, disclosing that following a "Type A" meeting with the FDA, the Company intended to re-submit its AXS-07 NDA by the third quarter of 2023. The press release further stated:

> The purpose of the Type A meeting was to obtain the FDA's feedback and agreement on the Company's plan to address the issues raised in the previously received Complete Response Letter (CRL) to support a resubmission of the AXS-07 NDA. The issues principally related to chemistry, manufacturing, and controls (CMC) considerations. Based on the FDA feedback, the Company will include new CMC information, including stability data on newly manufactured commercial scale batches of AXS-07, in its resubmission package. The resubmission package may also include additional clinical pharmacology information. The Company expects the NDA resubmission to be designated as Class 2 which would be subject to a six-month review. No additional clinical efficacy or safety trials have been requested by the FDA for a resubmission of the NDA.
>
> "We are very pleased with the outcome of the Type A meeting which clarifies our approach to resubmitting the NDA for AXS-07 for the acute treatment of migraine," said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. "We appreciate the FDA's thoughtful engagement and look forward to a successful resubmission.

90. Later, during a November 7, 2022, earnings conference call, in response to a question about Defendants' visibility into resubmitting the AXS-07 in the third quarter of 2023, Defendant Jacobson responded, the "FDA asked for a number of things from us, with respect to CMC, including stability data on new batches that had already been made, or are being made." Defendant Jacobson continued, describing that "stability data . . . is used to assess and inform the shelf life of an approved product. And there are various stability protocols that can be run, but typical ICH [ph] guidelines or at room temperature and accelerated conditions and those cannot

be sped up."[8] He added, "[a]nd so, typical times are 0, l month, 6 months, 12 months, et cetera," concluding that " it's just going through that process and generating those data."

91. In that comment, Defendants acknowledged that the CMC issues that caused the FDA to issue the CRL letter were several, including stability data on new batches. Defendants acknowledged that it was typical to apply the ICH guidelines to evaluate stability, requiring up to twelve months or more to complete, a process, according to Jacobson, that "cannot be sped up." Throughout the Class Period, however, among the warnings that Defendants issued relating to the timing of NDAs, in, for example, the Form 10-Q filed with the SEC for the quarter ended March 31, 2021 ("1Q2021 10-Q"), was:

> We may also experience numerous unforeseen events during, or as a result of, clinical trials and in the course of our preparation, submission, and review of NDA filings that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:
>
> ***
>
> in connection with the chemistry, manufacturing, and controls (CMC) data necessary for our NDA filing and approval, ***we will need to conduct stability studies*** and provide stability data to establish appropriate retest or expiration dating period;
>
> applicable to all future drug substance and drug product batches manufactured, packaged, and stored under similar circumstances, to establish the long-term storage conditions, and to provide evidence of the effect of various environmental conditions on the quality of the drug substance and drug product. Our product candidates may not demonstrate sufficient long-term stability to support an NDA filing or obtain approval, or the product shelf life may be limited by stability results[.][9]

[8] ICH guidelines refers to the protocols of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The categories of ICH guidelines include: quality; safety; efficacy; and multidisciplinary. The goal of ICH guidelines is to ensure safe, effective, and high quality of medicines produced worldwide. The ICH guidelines are applied by regulatory agencies

[9] Defendants disclosed this warning about the need to conduct stability studies for the first time in Axsome's Quarterly Report of Form 10-Q for the quarter ended September 30, 2019, filed with the SEC on November 7, 2019.

92. Further, in the 1Q2021 10-Q, Defendants warned that a manufacturer's failing to produce "product candidates in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers," may delay development and approval of products or the inability for the Company to meet demand. In relevant part, Defendants continued:

> We do not manufacture any of our product candidates, and we do not currently plan to develop any capacity to do so. We currently outsource all manufacturing of our product candidates to third parties typically without any guarantee that there will be sufficient supplies to fulfill our requirements or that we may obtain such supplies on acceptable terms. Any delays in obtaining adequate supplies with respect to our product candidates may delay the development or commercialization of our product candidates. Moreover, we do not yet have agreements established regarding commercial supply of our product candidates, and we may not be able to establish or maintain commercial manufacturing arrangements on commercially reasonable terms for any of our current or future product candidates for which we obtain approval in the future.
>
> We may not succeed in our efforts to establish manufacturing relationships or other alternative arrangements for any of our existing or future product candidates and programs. Our product candidates may compete with other products and product candidates for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that are both capable of manufacturing for us and willing to do so. If our existing third-party manufacturers, or the third parties that we engage in the future to manufacture a product for commercial sale or for our clinical trials, should cease to continue to do so for any reason, we likely would experience delays in obtaining sufficient quantities of our product candidates for us to meet commercial demand or to advance our clinical trials while we identify and qualify replacement suppliers. If for any reason we are unable to obtain adequate supplies of our product candidates or the drug substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively. Further, even if we do establish such collaborations or arrangements, our third-party manufacturers may breach, terminate, or not renew these agreements.
>
> Any problems or delays we experience in preparing for commercial-scale manufacturing of a product candidate may result in a delay in FDA approval of the product candidate or may impair our ability to manufacture commercial quantities or such quantities at an acceptable cost, which could result in the delay, prevention, or impairment of clinical development and commercialization of our product candidates and could adversely affect our business. ***For example, our manufacturers will need to produce specific batches of our product candidates to demonstrate acceptable stability under various conditions and for commercially***

> ***viable lengths of time. We and our contract manufacturers will need to demonstrate to the FDA and other regulatory authorities that this is acceptable stability data for our product candidates, as well as validate methods and manufacturing processes, in order to receive regulatory approval to commercialize any of our current or future product candidates***. Furthermore, if our commercial manufacturers fail to deliver the required commercial quantities of bulk drug substance or finished product on a timely basis and at commercially reasonable prices, we would likely be unable to meet demand for our products and we would lose potential revenues.

93. Prior to the Class Period, having demonstrated AXS-07's efficacy and safety through two Phase 3 clinical trials, Defendant Axsome, through Defendants Tabuteau and Jacobson, expressed its knowledge, understanding, and intense focus on CMC issues necessary to complete and to file the NDA. For example, on December 30, 2019, Axsome issued a press release, announcing positive results from AXS-07's Phase 3 MOMENTUM trial for the treatment of migraine. Defendant Tabuteau stated "[t]hese data have potentially important implications for patient care based on the high rate of inadequate response to and patient dissatisfaction with current treatments. With these positive results, we look forward to filing an NDA for AXS-07 in the acute treatment of migraine in 2020."

94. On March 12, 2020, Axsome issued a press, reporting the Company's fourth quarter and full year 2019 results and reiterating the positive AXS-07 clinical trial results and the Company's intention to file an NDA "in the fourth quarter of 2020." In an earnings conference call that same day, Defendant Tabuteau touted the positive clinical trial results for AXS-07, stating "With . . . two planned NDA filings Axsome is on track to transition to commercial stage potentially as early as next year."

95. Also on March 12, 2020, Axsome filed an annual report on Form 10-K with the SEC, reporting the Company's financial and operating results for the quarter and year ended December 31, 2019 ("2019 10-K"). Defendants Tabuteau and Pizzie signed the 2019 10-K. The 2019 10-K described Axsome's relationships with contract manufacturing organizations over

which the Company conducted "periodic audits of their facilities." About its CMOs, the Company stated, "[w]e believe that our existing suppliers of our product candidate active pharmaceutical ingredients and finished products will be capable of providing sufficient quantities of each to meet our clinical trial supply needs." Moreover, the Company provided boilerplate representations regarding Axsome's CMOs, stating that "[i]f the manufacturers upon whom we rely fail to produce our product candidates in the volumes that we require on a timely basis, . . . we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues." It continued, noting that CMOs ceasing to produce the Company's products would likely cause "delays in obtaining sufficient quantities of our product candidates for us to meet commercial demand or to advance our clinical trials while we identify and qualify replacement suppliers." The 2019 10-K concluded, "[i]f for any reason we are unable to obtain adequate supplies of our product candidates or the drug substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively."

96. With respect to CMC issues, the 2019 10-K provided only boilerplate representations regarding potential CMC issues that could materialize for any NDA filing, without addressing any CMC issues specific to the anticipated AXS-07 NDA filing. This standardized language stated that "the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional . . . [CMC], or other data and information." Similarly, Axsome stated generally that "[d]uring the course of review, the FDA may also request or require additional chemistry, manufacturing, and control (CMC), or other data and information, and the development and provision of these data and information may be time consuming and expensive."

97. On April 6, 2020, Axsome issued a press release touting that its INTERCEPT Phase 3 clinical trial met its primary endpoints "strengthen[ing] our planned NDA for AXS-07 . .

. which remains on track to be submitted to the FDA in the fourth quarter." On May 8, 2020, again, Axsome issued a press release affirming that it was "on track" to submit the AXS-07 NDA in the fourth quarter of 2020.

98. Also on May 8, 2020, Axsome hosted an earnings conference call. In response to an analyst question regarding whether there "[i]s . . . any new clinical data, including . . . CMC activities" for the Company's NDAs, Defendant Tabuteau stated:

> With regards to CMC activities, there are registration batches which are being manufactured now. A good thing for us is that we have been manufacturing our clinical trial supply at commercial scale and also at the same CMO that we're using for commercial production. So, there's no scale up that needs to be done.
>
> Now, with regards to manufacturing and any kind of science to it, there's always tweaks and experimentation, but I would say that there is no rate-limiting step and there is no extensive experimentation. This is simply manufacturing our registration batches for regulatory purposes.

99. On August 10, 2020, Axsome issued a press release, reporting the Company's second quarter 2020 results, reiterating that it was "on track to submit an NDA for AXS-07 . . . to the FDA in the fourth quarter of 2020," touting support for the NDA from positive efficacy results from Phase 3 clinical trials.

100. That same day, Axsome hosted an earnings conference call to discuss the Company's second quarter 2020 results. In his prepared remarks, Defendant Tabuteau boasted of "continu[ing] to advance our . . . AXS-07 product candidate[] towards NDA submission[] in . . . migraine[.]" Axsome he continued "remain[s] on track to submit the NDA for AXS-07 . . . in the fourth quarter." Defendant Tabuteau concluded, "[a]s we move towards the filing of our NDA[] in the fourth quarter . . . for AXS-07, our commercial team is focused on launch-readiness activities to ensure successful commercial execution," indicating his and Axsome's focus on issues beyond safety and efficacy with respect to the AXS-07 NDA and ultimate commercialization.

101. On November 5, 2020, Axsome issued a press release, disclosing that "Axsome now plans to submit the [AXS-07] NDA to the FDA in the first quarter of 2021, versus previous guidance of the fourth quarter of 2020, to allow for inclusion of supplemental manufacturing information to ensure a robust submission package." Thus, armed with positive safety and efficacy data from two Phase 3 clinical trials, by no later than late 2020, Defendants knew that CMC issues existed that caused Axsome to postpone submitting the AXS-07 NDA. Defendants, however, continued to assure investors about the success of AXS-07. For example, the November 5, 2020, press release continued that "[p]re-submission activities for the Company's NDA for AXS-07 in the acute treatment of migraine are progressing with major NDA-related items on track for completion by year-end." On the AXS-07 NDA, quoting Defendant Tabuteau, the November 5, 2020 press stated, "[o]ver the past several months, we continued to advance our . . . AXS-07 product candidate[] towards NDA submission[] in . . . migraine, and intensified our commercial launch readiness activities," and that "[w]e anticipate an active next few months as we complete our NDA submission[] for . . . AXS-07[.]"

102. Also on November 5, 2020, Axsome hosted an earnings conference call to discuss the Company's third quarter 2020 results. In his prepared remarks, Defendant Tabuteau reiterated that the Company was taking steps to ensure a robust AXS-07 NDA submission, particularly with respect to the drug's manufacturing. Manifesting his focus on NDA issues beyond safety and efficacy, with respect to the AXS-07 NDA, Defendant Tabuteau stated, "the major [NDA] related items are on track for completion by year end. We now plan to submit the NDA in the first quarter of 2021 versus previous guidance of the fourth quarter of 2020 in order to allow for inclusion of supplemental manufacturing information. We believe," he concluded, "that this approach will enhance the robustness of our submission."

103. On the same call, demonstrating the focus on existing manufacturing issues that impacted the AXS-07 NDA, in response to questions regarding the additional manufacturing information that Axsome submitted to the FDA for the AXS-07 NDA, Defendants Tabuteau and Jacobson assured investors that the additional information was just to ensure a robust submission and did not reflect any manufacturing issues. For example, in response to an analyst's questions about Axsome's submitting the AXS-07 NDA in the first quarter of 2021, "including extra manufacturing information, Defendant Tabuteau stated, with respect to AXS-07, by the end of the year, we will have completed all the major activities, which are needed to file our NDA. And we're on track to do that." He continued that "because of the unique manufacturing, behind the MoSEIC technology, we want to make sure that we have as robust as possible of a submission package. So we continue to generate data." Defendant Tabuteau then attributed the further delay in submitting the AXS-07 NDA to manufacturing data the Company wished to include in the NDA package, stating, "And the question is, how much do you include. And since, you know, we will be having some data in the early part of the year, we'd love to be able to include that in the package."

104. About those issues, during the November 5, 2020, conference call, Defendant Jacobson, expressing his own knowledge, understanding, and focus on the CMC issues, stated, "[s]o just want to be clear, this is not the result of the manufacturing or stability issue or anything like that." He continued, "[e]xactly as [Defendant Tabuteau] said, that we will have data available, that we think would add to the submission given us a novel delivery technology. And so that will just allow us to make the package as robust as possible."

105. The colloquy continued with an analyst asking "[c]ould you provide more specifics on what manufacturing data related to the MoSEIC platform will be added for AXS-07?" In response, Defendant Tabuteau stated, ". . .with regards to the additional manufacturing

information, this is [] standard information when you manufacture additional batches. So we continue to manufacture additional batches of drugs." He continued, "[a]nd while we already have very long-term stability data on other batches, we think that because of the unique nature of the delivery technology, this can only help to make the submission robust and assure that there are no hiccups during review." Thus, Axsome, Tabuteau, and Jacobson expressed their actual knowledge of and focus on issues relating to manufacturing AXS-07.

106. On March 1, 2021, Axsome issued a press release, reporting the Company's fourth quarter and full year 2020 results. The press release quoted Defendant Tabuteau as stating that "[w]e had successful pre-NDA meetings with the FDA . . . for AXS-07 in migraine." He continued that Axsome was "nearing submission of the NDA for AXS-07 in the acute treatment of migraine, which is expected early in the second quarter." Similarly, Tabuteau assured investors that "[o]ur focus for the remainder of the year will be on the regulatory activities surrounding these NDAs, [and] launch readiness to ensure a successful transition to commercialization[.]"

107. Also on March 1, 2021, Axsome hosted an earnings conference call with investors and analysts to discuss the Company's fourth quarter and full year 2020 results. On that call, and in response to an analyst's question regarding why the AXS-07 NDA submission was pushed back to second quarter 2021, Defendant Tabuteau stated, "With regard [AXS-]07 and the NDA filing the team remains on track to complete the filing by the end of the quarter. However, we are waiting on one vendor report which will slip into very beginning of the second quarter and that's the reason[.]"

108. Thus, with actual knowledge that Axsome "will need to conduct stability studies" (*supra* ¶ 91) Defendants knew, but omitted, that the Company's manufacturing facility—which was the same facility that it used for both trial and commercial production—was down, delaying

Axsome's timely receiving additional batches sufficient to conduct stability studies. Indeed, Defendant Tabuteau acknowledged in November 2020, as well as September and November 2022, that the additional stability studies that Axsome needed to complete were on new batches of AXS-07, but (as described by CW 1) as of early 2021, Axsome's available supply of AXS-07 was nearing expiration and it was unable to manufacture any new batches because of equipment problems. Moreover, the ICH guidelines Axsome followed could require at least six to twelve months, and possibly even longer, to complete those stability studies. This means that as of the start of the Class Period, the timeline for Axsome being able to make a complete NDA submission for AXS-07 was doubly delayed because even if it were able to resolve its indefinite manufacturing delay (which it was not able to do during the Class Period), the Company would then still need to first start the lengthy process of conducting stability studies on additional batches.

109. As of the start of the Class Period, Defendants therefore did not have sufficient runway to complete stability studies on new batches in advance of Axsome's filing the AXS-07 NDA. Axsome stated in its March 1, 2021, press release that it would submit the AXS-07 NDA in the second quarter of 2021 and ended up doing so in June 2021. Defendants, however, plainly followed their pattern of "cut[ting] corners" (*supra* ¶ 88) and submitted the AXS-07 NDA without having the ability to manufacture additional batches of AXS-07 or having even started stability studies on its nonexistent new batches of AXS-07. This conclusion is clear based on: Defendants' discussions shortly before the Class Period of the need to conduct stability studies on new batches of AXS-07 (*supra* ¶ 84); the prolonged manufacturing delay that the Company suffered during the Class Period that completely halted its ability to manufacture AXS-07 from at least April 2021 to when CW 1 left the Company in February 2022 (*supra* ¶¶ 73, 75, 98); the FDA's description of the Company's CMC problems as "unresolved" when it rejected the AXS-07 NDA in April 2022

(*supra* ¶¶ 52, 55); and the admission after the Class Period, in September and November 2022, that the FDA required "stability data on newly manufactured commercial scale batches of AXS-07" in the Company's resubmission of the NDA (*supra* ¶ 89).

C. AXS-05

110. CW 1 observed a separate issue in a study for AXS 05 caused by a poorly written testing protocol that allowed unqualified patients to participate in the relevant clinical study and resulted in Axsome receiving a Form 483 from the FDA for its failure to exclude unqualified patients from participating in the study.

111. Defendants should have been on heightened notice for CMC issues with AXS-07 because the Company had just experienced a similar issue with its other main product, AXS-05 for the treatment of MDD. Investors also expected that Axsome would not make the same mistake twice in a row and were shocked by the Company's repeated CMC failures on two consecutive NDAs in short succession.

112. For example, in an April 25, 2022 report, Cantor Fitzgerald lowered its price target for Axsome as a result of the news about the FDA's denial of the AXS-07 NDA, calling it "déjà vu," explaining that "[t]he Company ran into regulatory issues for its NDA of '05 for MDD as the agency had identified two deficiencies related to analytical methods in the CMC which needed to be addressed prior to the FDA taking action on the NDA. Although we had previously indicated that we believe these CMC issues have been resolved, our conviction that that is the case is now decreased as ***CMC deficiencies appear to be a persistent issue plaguing the company***."

113. Cowen also advised investors to "[r]ecall that the company had previously indicated that the FDA expected to complete the required inspection of the AXS-07 contract manufacturing facility prior to the April 30 PDUFA date and the company had not communicated any other delays with the review prior to today, thus the update comes as a disappointment. Additionally, given the

history of the AXS-05 review in MDD, investors are likely not to take kindly to any uncertaint[y] between the company and the FDA."

114. Also on April 25, 2022, Morgan Stanley published a note titled "Surprise Setback for AXS-07 in Migraine Presents Additional Pipeline Uncertainty." The note explained that "the surprise setback for AXS-07 is likely to increase investor uncertainty regarding prospects for the AXS-05 NDA - particularly given the hurdle faced by both applications are CMC related." As a result of this news, Morgan Stanley stated that "[w]e would expect significant pressure on AXSM following the update on AXS-07. We continue to remain on the sidelines with an EW rating, and note that our PT for AXSM is currently under review." It also described one of the primary risks that the Company faced as being an "FDA rejection of Axsome's NDA for AXS-07 in migraine."

115. Similarly, the SMBC Group commented in a note that day, titled "More Storm Clouds Gathering with Pending Rejection for AXS-07 in Migraine," that Axsome's stock suffered a 22% drop that day "on the negative news" and that "[w]e view the stock move as appropriate." This news would result in a "sizable delay" for the approval and launch of AXS-07, which led SMBC Group to lower its price target for Axsome from $45 per share to $29 per share. SMBC Group also commented that given Axsome's prior problems with AXS-05, regardless of whether the CMC problem with AXS-07 was "related to some of the problems that have been encountered previously with" AXS-05, "***troubles in manufacturing seem to be a recurring theme with AXSM's drug candidates***."

116. Axsome developed AXS-05 for the treatment of MDD, among other conditions. The Company states that it "believe[s] there is a substantial need for new, more effective treatments

for this large, underserved patient population." It describes AXS-05 as "a novel, oral, investigational NMDA receptor antagonist with multimodal activity."[10]

117. In July 2020, Axsome announced a positive pre-NDA meeting with the FDA regarding the Company's planned NDA submission of AXS-05 for the treatment of MDD. Axsome submitted the NDA for AXS-05 for MDD in early 2021.[11]

118. On April 26, 2021, Axsome announced that the FDA accepted the NDA for AXS-05 for MDD for priority review. This means that the FDA accelerated the review time from the standard 10 months to 6 months, making the Prescription Drug User Fee Act target action date August 22, 2021. The Company stated that "[t]he NDA is supported by results from two randomized, double-blind, controlled trials of AXS-05 in patients with a confirmed diagnosis of moderate to severe MDD."

119. Then, Axsome surprised investors by announcing before the market opened on August 9, 2021—less than two weeks before the August 22, 2021, PDUFA date for AXS-05 and just over a month before it submitted the NDA for AXS-07—that the FDA found "deficiencies" with the NDA. The Company stated in its August 9, 2021 press release that "[a]s part of the ongoing review of our NDA for AXS-05, the FDA recently notified us that they have identified deficiencies that preclude labeling discussions at this time." The Company added, "[w]e are attempting to learn the nature of these deficiencies with the goal of addressing them, however, this development may lead to a delay in the potential approval of AXS-05."

120. The August 9, 2021, press release continued, explaining that "[o]n July 30, 2021, the Company received a letter from the FDA stating that it has identified deficiencies that preclude

[10] An NMDA receptor is a type of neurological receptor.

[11] Axsome announced on March 1, 2021, that it submitted the NDA earlier that year, but did not provide the specific date.

discussion of labeling and post-marketing requirements/commitments at this time." With respect to FDA approval, the Company concluded, "[t]he letter stated further that the notification does not reflect a final decision on the information under review. The letter did not state what the deficiencies are."[12]

121. On the Company's August 9, 2021, earnings call, Defendant Tabuteau acknowledged that "[a]lthough the [FDA] letter stated that the notification does not reflect a final decision on the information under review, this development may lead to a delay in the potential approval of AXS-05. We will keep you informed as we learn more."

122. Investors reacted negatively to this news because it meant that, at the very least, there would be a material delay in the approval of AXS-05. For example, Guggenheim Securities issued a report warning investors that "AXS-05 approval now in question after FDA letter noting 'deficiencies' in the NDA filing."

123. On August 9, 2021, Axsome's stock price fell by 46.5%, from a closing price of $51.16 per share the day before to a closing price of $27.37 that day.

124. Following this time, based on their public statements, Defendants knew—even in the face of Phase 3 clinical trials that met endpoints for safety and efficacy of its drug candidates—that the FDA might not approve Axsome's Applications because of CMC issues. At the time, AXS-07 was the Company's only other product to have had an NDA submitted. Moreover, while Axsome had the opportunity to fix the CMC issues with AXS-05 under its original NDA, the CMC issues with AXS-07 were even more serious because they led to the FDA's issuing a CRL denying

[12] The FDA explains that post-marketing requirements and commitments are "studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use." While these studies are not completed until after approval, they may be set out as part of the approval process.

the drug's Application. Defendants expressed publicly that Axsome was attuned to CMC problems following the CMC issues that the FDA raised with AXS-05.

125. On August 23, 2021, the Company updated investors, stating that the FDA "informed the Company in a teleconference on August 20, 2021, that its review of the new drug application (NDA) for AXS-05 for the treatment of major depressive disorder would not be completed by the PDUFA target action date of August 22, 2021. The FDA did not request additional information from the Company, and the review of the application is ongoing."

126. On November 8, 2021, during Axsome's earnings call for the third quarter of 2021, Defendant Tabuteau disclosed that the FDA "recently informed us of two deficiencies related to analytical methods in the chemistry, manufacturing and control section of the NDA [for AXS-05], which must be addressed prior to the FDA taking action on the NDA."

V. DEFENDANTS' MATERIALLY FALSE AND MISLEADING STATEMENTS DURING THE CLASS PERIOD

127. The Class Period begins on May 10, 2021, when Axsome hosted a conference call with investors and analysts to discuss the Company's first quarter 2021 results. Defendants Tabuteau, Jacobson, Pizzie, and O'Gorman attended this call. In response to an analyst question regarding "what the gating factors are in terms of getting th[e AXS-07 NDA] submission into the FDA" given that Axsome had pushed back its regulatory timeline multiple times, Defendant O'Gorman stated, in relevant part: "With regards to AXS-07, we're very much on track to file the NDA this quarter, as we've previously stated, and there really isn't any update there. The team is working diligently to make sure that we have a timely, but also a quality filing."

128. The foregoing statement about being on track to file the AXS-07 NDA was materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that: (i) Axsome's

development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce AXS-07) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07 before it belatedly (after repeated delays in the initially represented timeline) submitted its AXS-07 NDA in June 2021; and (iii) as a result, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the AXS-07 NDA was not "on track" and the FDA would delay or even reject approval of the AXS-07 NDA because of the unresolved material CMC issues and resulting delay in stability studies.

129. Also on May 10, 2021, Axsome filed the 1Q2021 10-Q. Defendants Tabuteau and Pizzie signed the 1Q2021 10-Q and the certifications pursuant to the Sarbanes-Oxley Act of 2002 ("SOX") attesting to the accuracy of the statements therein. Warning of the "time consuming and inherently unpredictable" FDA approval process, the 1Q2021 10-Q stated, "[d]uring the course of review, the FDA may also request or require additional CMC, or other data and information, and the development and provision of these data and information may be time consuming and expensive." The 1Q2021 10-Q added, "in connection with the chemistry, manufacturing, and controls (CMC) data necessary for our NDA filing and approval, we will need to conduct stability studies and provide stability data to establish appropriate retest or expiration dating period."

130. The foregoing statements warning about the FDA's requiring additional CMC information in the context of stability studies supporting the AXS-07 NDA, were materially false and misleading because of the CMC problems that at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing Axsome was already

experiencing that made it completely unable to manufacture AXS-07. In addition, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the AXS-07 NDA would require stability studies that Axsome had not yet begun because of this manufacturing delay. Later, with respect to why resubmission of the AXS-07 NDA would extend into the second half of 2023 in order to provide the information the FDA requested, Defendant Jacobson stated in Axsome's November 7, 2022, earnings conference call, "and there are various stability protocols that can be run, but typical ICH guidelines or at room temperate and accelerated conditions and those cannot be sped up." Jacobson continued, "and so, typical times are 0, 1 month, 6 months, 12 months, et cetera. So it's just going through that process and generating those data." By May, 2021, therefore, Defendants knew, but recklessly disregarded that the typical ICH guidelines Axsome applied for assessing stability could not be rushed and required 12 months or more. As such, in addition to knowing or recklessly disregarding that that Axsome's CMO was unable to produce AXS-07, Defendants knew or recklessly disregarded that stability tests could not conclude timely to support the NDA, almost certainly resulting in the FDA delaying or rejecting approval of AXS-07.

131. In addition, the 1Q2021 10-Q incorporated, by reference, information from Axsome's 2020 10-K.[13] Thus, the 1Q2021 10-Q reiterated Defendants' belief that "existing suppliers of our product candidate active pharmaceutical ingredients and finished products will be capable of providing sufficient quantities of each to meet our clinical trial supply needs." Defendants further warned that "[i]f the manufacturers upon whom we rely fail to produce our

[13] The 1Q2021 10-Q stated, "You should read the following discussion and analysis . . . in conjunction with management's discussion and analysis and the audited consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2020. . . ." Axsome filed the 2020 10-K on March 1, 2021.

product candidates in the volumes that we require on a timely basis, . . . we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues." Defendants warned that "[i]f our existing third-party manufacturers, or the third parties that we engage in the future to manufacture a product for commercial sale or for our clinical trials, should cease to continue to do so for any reason, we likely would experience delays in obtaining sufficient quantities of our product candidates for us to meet commercial demand or to advance our clinical trials while we identify and qualify replacement suppliers." The 2020 10-K continued that "if for any reasons [Axsome is] unable to obtain adequate supplies of our product candidates or the drug substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively."

132. The foregoing statements warning about potential problems with manufacturers, including those who manufactured AXS-07, were materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson and Laliberte knew or were severely reckless in not knowing facts they omitted that, in context, did not fairly aligns with the information in their possession at that time, including that: (i) Axsome's development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce AXS-07) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07 before it belatedly (after repeated delays in the initially represented timeline) submitted its AXS-07 NDA in June 2021; and (iii) as a result, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the Axsome had already experienced the problems with AXS-07 manufacturing

about which it had warned, materially increasing the likelihood of delaying or preventing FDA approval and undermining their statement that their contract manufacturer for AXS-07 was or would be capable of adequate production.

133. On August 9, 2021, Axsome hosted a conference call with investors and analysts to discuss the Company's second quarter 2021 results in which, among others, Defendants Tabuteau and Jacobson participated on behalf of Axsome. Probing about the manufacturing problems that had materially slowed FDA approval and commercialization of AXS-05, an analyst noted that AXS-07 is manufactured at the same facility as AXS-05. In response, Defendant Jacobson stated:

> So for the manufacturing process for AXS-07, that actually is a bit more complicated and there are two facilities that we utilized for the manufacturer of the drug product. The drug -- the API's are also available under open DMF too in the U.S. And of the two facilities that we used for drug product manufacturing, one of them is the same that we used for AXS-05.

134. The foregoing statement about AXS-07's manufacturer was materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that: (i) Axsome's development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce AXS-07) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07; (iii) as a result, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the AXS-07 NDA was not "on track" and the FDA would delay or even reject approval of the AXS-07 NDA because of the unresolved material CMC issues. Defendants Axsome, Tabuteau,

Jacobson, and Laliberte misrepresented the status of CMC issues with AXS-07 by discussing the manufacturing of AXS-07 while omitting the material CMC issues that had cause and would cause further, material delay in obtaining approval and commercializing AXS-07.

135. Also on August 9, 2021, Axsome filed with the SEC a quarterly report on Form 10-Q, reporting the Company's financial and operating results for the quarter ended June 30, 2021 ("2Q2021 10-Q"). The 2Q2021 10-Q was signed by and contained SOX certifications from, Defendants Tabuteau and Pizzie. Warning of the "time consuming and inherently unpredictable" FDA approval process, the 2Q2021 10-Q stated, "[d]uring the course of review, the FDA may also request or require additional CMC, or other data and information, and the development and provision of these data and information may be time consuming and expensive." The 2Q2021 10-Q added, "in connection with the chemistry, manufacturing, and controls (CMC) data necessary for our NDA filing and approval, we will need to conduct stability studies and provide stability data to establish appropriate retest or expiration dating period."

136. The foregoing statements warning about the FDA's requiring additional CMC information in the context of stability studies supporting the AXS-07 NDA, were materially false and misleading because of the CMC problems that at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing Axsome was already experiencing that made it completely unable to manufacture AXS-07. In addition, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the AXS-07 NDA would require stability studies that Axsome had not yet begun because of this manufacturing delay. Later, with respect to why resubmission of the AXS-07 NDA would extend into the second half of 2023 in order to provide the information the FDA requested, Defendant Jacobson stated in Axsome's November 7, 2022, earnings conference call, "and there

are various stability protocols that can be run, but typical ICH guidelines or at room temperate and accelerated conditions and those cannot be sped up." Jacobson continued, "and so, typical times are 0, 1 month, 6 months, 12 months, et cetera. So it's just going through that process and generating those data." By May, 2021, therefore, Defendants knew, but recklessly disregarded that the typical ICH guidelines Axsome applied for assessing stability could not be rushed and required 12 months or more. As such, in addition to knowing or recklessly disregarding that that Axsome's CMO was unable to produce AXS-07, Defendants knew or recklessly disregarded that stability tests could not conclude timely to support the NDA, almost certainly resulting in the FDA delaying or rejecting approval of AXS-07.

137. In addition, the 2Q2021 10-Q incorporated, by reference, information from Axsome's 2020 10-K. Thus, the 2Q2021 10-Q reiterated Defendants' belief that "existing suppliers of our product candidate active pharmaceutical ingredients and finished products will be capable of providing sufficient quantities of each to meet our clinical trial supply needs." Defendants further warned that "[i]f the manufacturers upon whom we rely fail to produce our product candidates in the volumes that we require on a timely basis, . . . we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues." Defendants warned that "[i]f our existing third party manufacturers, or the third parties that we engage in the future to manufacture a product for commercial sale or for our clinical trials, should cease to continue to do so for any reason, we likely would experience delays in obtaining sufficient quantities of our product candidates for us to meet commercial demand or to advance our clinical trials while we identify and qualify replacement suppliers." The 2020 10-K continued that "if for any reasons [Axsome is] unable to obtain adequate supplies of

our product candidates or the drug substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively."

138. The foregoing statements warning about potential problems with manufacturers, including those who manufactured AXS-07 were materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing facts they omitted that, in context, did not fairly align with the information in their possession at that time, including that: (i) Axsome's development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce sufficient supply of AXS-07 even for limited clinical trials) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07; and (iii) as a result, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that Axsome had already experienced the problems with AXS-07 manufacturing about which it had warned, materially increasing the likelihood that the FDA would delay or even reject approval of the AXS-07 NDA because of the unresolved material CMC issues undermining their opinion that their contract manufacturer to AXS-07 was or would be capable of adequate production.

139. On September 14, 2021, Axsome issued a press release by Defendant Jacobson and filed on a Form 8-K signed by Defendant Tabuteau, announcing that the FDA had accepted the AXS-07 NDA, stating:

> The NDA is supported by results from two Phase 3 randomized, double-blind, controlled trials of AXS-07 in the acute treatment of migraine, the MOMENTUM

> and INTERCEPT trials, which demonstrated statistically significant elimination of migraine pain with AXS-07 compared to placebo and active controls.

140. The foregoing statement about the AXS-07 NDA and the support from the two Phase 3 clinical trials was materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson and Laliberte knew or were severely reckless in not knowing that: (i) Axsome's development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce AXS-07) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07; and (iii) as a result the FDA would delay or even reject approval of the AXS-07 NDA because of the unresolved material CMC issues. Defendants Axsome, Tabuteau, Jacobson and Laliberte misrepresented the likelihood that the FDA would approve the NDA for AXS-07 in light of the CMC problems that plagued the development of AXS-07.

141. On November 8, 2021, Axsome announced that "[t]he FDA notified the Company that, due to COVID-19 pandemic-related travel restrictions, they may be unable to complete a required inspection of a contract manufacturing facility [for the AXS-07 NDA] . . . prior to the PDUFA date[.]" Later that day, Axsome hosted an earnings conference call with investors and analysts to discuss the Company's third quarter 2021 results. On that call, in response to an analyst question regarding the FDA's delaying the inspection of the contract manufacturing facility for AXS-07 that Axsome had announced that day, Defendants Tabuteau and Laliberte, manifesting their knowledge of and focus on manufacturing issues relating to the AXS-07 NDA, downplayed their impact on the drug's regulatory timeline. After Tabuteau called the FDA's delay in inspecting manufacturing facilities "straightforward," Laliberte stated:

> Thanks for that question. So there are obviously multiple manufacturing sites involved in the process for AXS-07. The FDA notified us that one specific manufacturing location that is based in the United States is required to have an inspection prior to them, as part of the review process.
>
> And then they did notify us that because of COVID-related restrictions, that may be in jeopardy of happening before the PDUFA date. So it's just this one manufacturer based in the United States that they specifically notified us of in their communication.

142. Also during the November 8, 2021, conference call, urged on by Defendant Tabuteau, Defendant Laliberte denied that issues with AXS-07's manufacturing might delay FDA approval, stating that "because [AXS-05 and AXS-07] are distinct molecules with different active components, [the same analytical measure on the manufacturing level] would not carry over necessarily into the 07 application specifically."

143. The foregoing statements about manufacturing issues relating to the AXS-07 NDA were materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson and Laliberte knew or were severely reckless in not knowing that: (i) Axsome's development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce AXS-07) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07; and (iii) as a result, the FDA would delay or even reject approval of the AXS-07 NDA because of the unresolved material CMC issues. In the context of their discussing the impact of manufacturing issues on the NDA for AXS-07, Defendants Axsome, Tabuteau, Jacobson, and Laliberte were duty bound to disclose that material CMC issues impacted the development of AXS-07 and its prospects and timing for approval.

144. Also on November 8, 2021, Axsome filed a quarterly report on Form 10-Q with the SEC, reporting the Company's financial and operating results for the quarter ended September 30, 2021 ("3Q2021 10-Q"). The 3Q2021 10-Q was signed by and contained SOX certifications from, Defendants Tabuteau and Pizzie.

145. Warning of the "time consuming and inherently unpredictable" FDA approval process, the 3Q2021 10-Q stated, "[d]uring the course of review, the FDA may also request or require additional CMC, or other data and information, and the development and provision of these data and information may be time consuming and expensive." The 3Q2021 10-Q added, "in connection with the chemistry, manufacturing, and controls (CMC) data necessary for our NDA filing and approval, we will need to conduct stability studies and provide stability data to establish appropriate retest or expiration dating period." The 3Q2021 10-Q also disclosed that "[t]he FDA has set a PDUFA target action date for the AXS-07 NDA of April 30, 2022."

146. The foregoing statements warning about the FDA's requiring additional CMC information in the context of stability studies, supporting the AXS-07 NDA, were materially false and misleading. No later than April 2021, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the AXS-07 NDA would require stability studies that Axsome was not able to begin as planned because of its inability to manufacture AXS-07. Later, with respect to why resubmission of the AXS-07 NDA would extend into the second half of 2023 in order to provide the information the FDA requested, Defendant Jacobson stated in Axsome's November 7, 2022, earnings conference call, "and there are various stability protocols that can be run, but typical ICH guidelines or at room temperate and accelerated conditions and those cannot be sped up." Jacobson continued, "and so, typical times are 0, 1 month, 6 months, 12 months, et cetera. So it's just going through that process and generating those data."

By May, 2021, therefore, Defendants knew, but recklessly disregarded that the typical ICH guidelines Axsome applied for assessing stability could not be rushed and required 12 months or more. As such, in addition to knowing or recklessly disregarding that that Axsome's CMO was unable to produce AXS-07, Defendants knew or recklessly disregarded that stability tests could not conclude timely to support the NDA, almost certainly resulting in the FDA delaying or rejecting approval of AXS-07. In addition, by noting the upcoming PDUFA date, the statements in the 3Q2021 10-Q even further misled investors by failing to disclose the problems with the manufacturing of AXS-07 that would preclude FDA approval by that date.

147. In addition, the 3Q2021 10-Q incorporated, by reference, information from Axsome's 2020 10-K. Thus, the 3Q2021 10-Q reiterated Defendants' belief that "existing suppliers of our product candidate active pharmaceutical ingredients and finished products will be capable of providing sufficient quantities of each to meet our clinical trial supply needs." Defendants further warned that "[i]f the manufacturers upon whom we rely fail to produce our product candidates in the volumes that we require on a timely basis, . . . we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues." Defendants warned that "[i]f our existing third party manufacturers, or the third parties that we engage in the future to manufacture a product for commercial sale or for our clinical trials, should cease to continue to do so for any reason, we likely would experience delays in obtaining sufficient quantities of our product candidates for us to meet commercial demand or to advance our clinical trials while we identify and qualify replacement suppliers." The 2020 10-K continued that "if for any reasons [Axsome is] unable to obtain adequate supplies of our product candidates or the drug substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively."

148. The foregoing statements warning about potential problems with manufacturers, including those who manufactured AXS-07 were materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson and Laliberte knew or were severely reckless in not knowing facts they omitted that, in context, did not fairly align with the information in their possession at that time, including that: (i) Axsome's development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce sufficient supply of AXS-07 even for limited clinical trials) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07; and (iii) as a result, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the Axsome had already experienced the problems with AXS-07 manufacturing about which it had warned, materially increasing the likelihood that the FDA would delay or approval of the NDA and undermining their statement that their contract manufacturer for AXS-07 was or would be capable of adequate production.

149. On March 1, 2022, Axsome issued a press release by Defendant Jacobson, and filed with the SEC on a Form 8-K signed by Defendant Tabuteau, reporting the Company's fourth quarter and full year 2021 results. In the context of the AXS-07 NDA and the FDA's informing Defendants that the COVID-19 pandemic may disable the FDA from investigating the relevant contract manufacturing facility, Defendants stated that "***Axsome has since been informed by the FDA that it does not anticipate any issues with completing this facility inspection prior to the AXS-07 PDUFA date***." The same March 1, 2022, press release quoted Defendant Tabuteau as stating that "2021 was a year of continued progress which has put us in a position to potentially

launch two new investigational medicines for patients living with depression and migraine," including "the April 30 PDUFA date for our NDA for AXS-07 in the acute treatment of migraine [that] is approaching."

150. The foregoing statements about the manufacturing of AXS-07 and its potential launch were materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that material CMC problems impacted the NDA for AXS-07, rendering FDA approval unlikely. In addition, Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or recklessly disregarded that their statements omitted that: (i) Axsome's development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce AXS-07) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07; and (iii) as a result, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the Axsome had already experienced the problems with AXS-07 manufacturing about which it had warned, materially increasing the likelihood of delaying or confounding FDA approval.

151. Also on March 1, 2022, Axsome filed an annual report on Form 10-K with the SEC, reporting the Company's financial and operating results for the quarter and year ended December 31, 2021 (the "2021 10-K"). The 2021 10-K was signed by and contained SOX certifications from Defendants Tabuteau and Pizzie.

152. In the 2021 10-K, Defendants stated, "[w]e believe that our existing suppliers of our product candidate active pharmaceutical ingredients and finished products will be capable of

providing sufficient quantities of each to meet our clinical trial supply needs." This statement was particularly false and misleading because Defendants knew about manufacturing problems with Axsome's "existing suppliers" for a planned study and therefore did not "believe that our existing suppliers . . . will be capable of providing sufficient quantities of each to meet our clinical trial supply needs."

153. The foregoing statements warning about potential problems with manufacturers, including those who manufactured AXS-07, were materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson and Laliberte knew or were severely reckless in not knowing facts they omitted that, in context, did not fairly aligns with the information in their possession at that time, including that: (i) Axsome's development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce AXS-07) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07; and (iii) as a result, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the Axsome had already experienced the problems with AXS-07 manufacturing about which it had warned, materially increasing the likelihood that the FDA would delay or reject approval and undermining their statement that their contract manufacturer to AXS-07 was or would be capable of adequate production.

154. The 2021 10-K also stated that "[i]f the manufacturers upon whom we rely fail to produce our product candidates in the volumes that we require on a timely basis, . . . we may face delays in the development and commercialization of, or be unable to meet demand for, our

products and may lose potential revenues" and that "[i]f our existing third-party manufacturers, or the third parties that we engage in the future to manufacture a product for commercial sale or for our clinical trials, should cease to continue to do so for any reason, we likely would experience delays in obtaining sufficient quantities of our product candidates for us to meet commercial demand or to advance our clinical trials while we identify and qualify replacement suppliers." While Axsome framed these statements as "risks related to our dependence on third parties," they were materially misleading because Defendants described them as potential future issues when, in fact, Axsome was already precisely experiencing these problems with its third-party manufacturer for AXS-07.

155. The foregoing statements warning about the manufacturing of AXS-07 as it impacted development and commercialization of the product were materially false and misleading. No later than April, 2021, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that: (i) Axsome's development of AXS-07 encountered material CMC problems (including that Axsome's CMO was unable to produce AXS-07) that Defendants were required to disclose in the context of discussions of CMC issues or positive disclosures about clinical trial results and assurances as to the filing of, and FDA approval for, the AXS-07 NDA; (ii) Axsome was unable to resolve these CMC problems or complete stability studies on additional batches of AXS-07; and (iii) as a result, at least Defendants Axsome, Tabuteau, Jacobson, and Laliberte knew or were severely reckless in not knowing that the Axsome had already experienced the problems with AXS-07 manufacturing about which it had warned, materially increasing the likelihood that the FDA would delay or reject approval.

VI. THE TRUTH BEGINS TO EMERGE

156. Defendants' wrongful conduct, as alleged herein, directly and proximately caused the economic loss suffered by Plaintiffs and the Class.

157. Throughout the Class Period, the price of Axsome common stock was artificially inflated and/or maintained at an artificially high level as a result of Defendants' materially false and misleading statements and omissions identified herein.

158. The price of Axsome's common stock significantly declined when the misrepresentations made to the market, and/or the information and risks alleged herein to have been concealed from the market, and/or the effects thereof, materialized and/or were revealed, causing investors' losses. As a result of Defendants' wrongful acts and omissions, and the precipitous decline in the market value of Axsome's common stock, Plaintiffs and other Class members have suffered significant losses and damages.

159. In particular, the corrective disclosure described below revealed that despite Defendants' many misrepresentations concerning the purportedly strong support for the submission and approval of the NDA for AXS-07, problems with Axsome's manufacturing process for AXS-07 caused the Company to delay the submission of the NDA and then caused the FDA to issue a CRL for the NDA.

160. On April 25, 2022, before the market opened, Axsome filed a Form 8-K with the SEC, which disclosed:

> On April 22, 2022, Axsome . . . was informed by the [FDA] that [CMC] issues identified during the FDA's review of the Company's [NDA] for its AXS-07 product candidate for the acute treatment of migraine are unresolved. Based upon the time remaining in the NDA review cycle, the Company expects to receive a [CRL] with respect to this NDA on or about the [PDUFA] target action date of April 30, 2022.

161. On this news, Axsome's stock price plunged $8.60 per share, or 21.99%, to close at $30.50 per share on April 25, 2022, on trading volume that was over 2.7 times the 20-day moving average.

162. The abundant analyst commentary described above shows how surprised investors were to learn that the FDA would not be approving the NDA for AXS-07 because of CMC issues. (*See supra* ¶¶ 54, 112-15).

163. For example, William Blair published a report that described this news as "obviously disappointing," noting that the stock is down 24% premarket.

164. As a result of Defendants' wrongful acts and omissions, and the precipitous decline in the market value of the Axsome's common stock, Plaintiffs and other Class members have suffered significant losses and damages.

VII. ADDITIONAL SCIENTER ALLEGATIONS

165. Defendants each had scienter as to the false and misleading nature of their statements because they each knew or, at a minimum, recklessly disregarded the facts described above in the Substantive Allegations section of this amended complaint.

166. Defendants Tabuteau and Pizzie's actual knowledge of the falsity of the alleged misstatements and omissions is also established by their signing of the SOX certifications, that certified each of Axsome's SEC filings, among other things, "does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report"; fully complies with the requirements of Section 13(a) or 15(d) of the [Exchange Act], as amended"; and that "[t]he information contained in [them] fairly presents, in all material respects, the financial condition and results of operations of the Company."

Before vouching for the accuracy of the statements made in Axsome's SEC filings, the certifying Defendants were obligated to familiarize themselves with the contents of the filings and Axsome's the underlying operations described therein.

167. Defendants' scienter is further established by Axsome's announcement on November 5, 2020 that "Axsome now plans to submit the [AXS-07] NDA to the FDA in the first quarter of 2021, versus previous guidance of the fourth quarter of 2020, to allow for inclusion of supplemental manufacturing information to ensure a robust submission package."

168. Defendants Tabuteau and Jacobson in particular had knowledge of these manufacturing issues because they discussed this issue on the Company's conference call that day, including Tabuteau noting the continued "manufactur[ing of] additional batches of drugs."

169. Defendants Tabuteau and Jacobson also showed their knowledge of the CMC issues with AXS-07 by discussing them on the Company's May 2, 2022, conference call following the FDA's issuance of its CRL.

170. In addition, Defendants' scienter is shown by Axsome's announcement on April 25, 2022, that the CMC issues that the FDA identified during its review of the Company's NDA for AXS-07 were "unresolved." This language indicates that the FDA had previously discussed these issues with the Company and provided this update in April 2022 because the problems remained unresolved.

171. Defendants' scienter is further established because they were on notice of CMC issues with AXS-07 based on the Company's similar prior experience with AXS-05. As analysts noted when the CMC problems with AXS-07 were announced on April 25, 2022, this was "déjà vu" because "[t]he Company ran into regulatory issues for its NDA of '05 for MDD," "***CMC***

deficiencies appear to be a persistent issue plaguing the company" and "***troubles in manufacturing seem to be a recurring theme with AXSM's drug candidates.***"

172. Defendants' scienter is further established by the FDA's description of their personal involvement in Axsome's drug development process. In June 2021, the FDA inspected one of Axsome's facilities.[14] The FDA's report from this inspection, dated July 1, 2021, noted that Defendant Tabuteau "identified himself as the most responsible person" for the Company. In addition, Tabuteau told the inspector that "as the founder of Axsome Therapeutics, Inc., he is and has been involved[d] in almost every aspect associated with the development, implementation, and realization of [redacted] drug development projects." These responsibilities include, but are not limited to:

- "Correspondence and interaction with FDA regulatory officials";
- "Initial and continuing product development and regulatory strategies";
- "Clinical development and clinical trial outlook and implementation";
- "Protocol development and review";
- "Budget and finance";
- "IND and NDA filings"; and
- "Oversight [of] all company departments and personnel."

173. This inspection report also stated that as "the most responsible person," Defendant Tabuteau "has oversight over the following five key product development departments: [1] Quality assurance/product strategy, headed by executive VP Kevin J. Laliberte," (2) "Operations, headed by the chief operational officer, Mark l. Jacobsen," (3) "Clinical development, headed by senior

[14] Plaintiffs append hereto as Exhibit 1 a copy of this inspection report that is available on the website https://fdazilla.com/. CW 3 (described below) identified this inspection as related to AXS-05.

VP, Ms. Amanda E. Jones," (4) "Finance, headed by the chief financial officer" Nick Pizzie, and (5) "Commercial, headed by Lori A. Engelbert, Executive VP, commerce, and business development."

174. Defendants Jacobsen, O'Gorman, and Laliberte also participated in this inspection. The report described Jacobsen as the Company's Chief Operating Officer and Laliberte as its Executive Vice President of Product Strategy.

175. Defendant Laliberte told the inspector "that his responsibilities include overseeing multiple departments[,] including regulatory, chemistry manufacturing and controls, pharmacovigilance, supply chain, medical affairs, and research and operations." The report also noted elsewhere that individuals on the Company's CMC team report to Laliberte. Defendant Laliberte reports to Defendant Tabuteau.

176. The report described Defendant O'Gorman as the Senior Vice President of Medical Affairs who reports to Defendant Tabuteau. O'Gorman told the inspector that his "responsibilities include overseeing and providing medical monitoring services, safety meetings, and evaluation of adverse events and adverse events reports."

177. As noted above, CW 1 reported to the Executive Director of Clinical Research (Amanda Jones), the Director of Clinical Operations (Cheryl Askew), and the Senior Director of Clinical Operations (Caroline Streicher) at various points during CW 1's tenure at the Company. Jones, Askew, and Streicher all participated in the June 2021 FDA inspection.

178. The report described Jones as "one of the key points of" contact during the inspection. She told the inspector that her responsibilities included overseeing product development, "third party vendor qualification and management," and responsibilities related to clinical studies. Jones reports to Defendant Tabuteau.

179. This organizational structure corroborates CW 1's descriptions of the Company and shows even further that Defendant Tabuteau would be aware of the items that CW 1 observed.

180. Defendants Jacobson's and Laliberte's scienter is further supported by CW 1's recounting that Fang Liu, who oversaw Axsome's inability to manufacture AXS-07 because of equipment problems, reported to Defendants Jacobson and Laliberte and provided them updates about the status of drug supplies.

181. In addition, Defendant Laliberte's scienter is supported by CW 1's description of Axsome's internal audit in the summer of 2021 of Axsome's CMC operations and manufacturing facilities, in preparation of the FDA's review as part of the NDA process for AXS-07 and AXS-05, that raised equipment problems at Axsome's manufacturing facilities. Defendant Laliberte was involved in responding to these issues and specifically discussed them at an internal meeting.

182. Defendants' scienter is further shown by CW 1's assessment that executive management would have known about the equipment problems that Axsome's vendor was having with manufacturing AXS-07.

183. Furthermore, Defendants' scienter is corroborated by CW 1's observation that the Company's executive leadership appeared to prioritize profit over patients, they "cut corners," and they seemed to always be in a rush to meet milestones.

184. In addition, Defendants' scienter is further corroborated by a former employee who worked at Axsome from September 2018 to September 2021 in Clinical Operations ("CW 3") and reported to Amanda Jones, the Senior VP of Clinical Development. CW 3 had a senior role in Clinical Operations and participated in the June 2021 FDA inspection that was the subject of the report discussed above. According to CW 3, Axsome's top leadership was "extremely secretive" and not forthcoming internally about Axsome's interactions with the FDA. CW 3 was not even

told when the Company submitted its NDAs for AXS-05 and AXS-07. This clandestine attitude among Axsome's top leadership and their and unwillingness to share information internally regarding its NDAs and interactions with the FDA even with senior employees, demonstrate the senior executives' high level of personal involvement in these matters.

185. Defendant Jacobson's scienter is further supported by his acknowledgment in November 7, 2022, that stability studies could take a full year, yet Axsome could not even start the lengthy stability studies that it was required to do on new batches of AXS-07 while it was unable to manufacture those batches because of equipment problems that started in early 2021.

186. The Individual Defendants' scienter is also established because the alleged misstatements and omissions at issue here concerned Axsome's core operations. Indeed, Axsome described AXS-07 is one of its five products from its "core CNS portfolio." Moreover, AXS-07 is one of only two drugs for which Axsome had submitted an NDA through the Class Period, that Axsome planned to commercialize in the near future, and that contributed in any meaningful way to market analysts' valuation of the Company. In addition, CMC issues are a crucial part of an NDA filing. Furthermore, the type of problems that CW 1 noted, where equipment problems prevented AXS-07's complex manufacturing process from operating for an extended period of time coinciding with the NDA submission for AXS-07, is the type of severe problem that would be brought to the attention of the Company's senior executives. Defendants, by virtue of their roles in senior management and involvement in the Company's core operations, would have had knowledge of the true nature of the Company's core businesses during the Class Period. In addition, Defendants had access to reports and communications describing these operations.

187. Axsome itself had scienter as to the false and misleading nature of the statements described above based on the knowledge of the Individual Defendants. In addition, because the

false and misleading statements at issue here relate to one of the Company's core products, the Company's scienter can be inferred because these statements would have been approved by corporate officials that knew they were false or misleading.

VIII. NO SAFE HARBOR

188. The statutory safe harbor provided for forward-looking statements under certain circumstances does not apply to any of the allegedly false statements pleaded in this Complaint. The statements alleged to be false and misleading herein all relate to then-existing facts and conditions. In addition, to the extent certain of the statements alleged to be false may be characterized as forward looking, they were not identified as "forward-looking statements" when made and there were no meaningful cautionary statements identifying important factors that could cause actual results to differ materially from those in the purportedly forward-looking statements.

189. In the alternative, to the extent that the statutory safe harbor is determined to apply to any forward-looking statements pleaded herein, Defendants are liable for those false forward-looking statements because at the time each of those forward-looking statements was made, the speaker had actual knowledge that the forward-looking statement was materially false or misleading, and/or the forward-looking statement was authorized or approved by an executive officer or top management of Axsome who knew that the statements were false when made.

IX. CLASS ACTION ALLEGATIONS

190. Plaintiffs bring this action as a class action pursuant to Federal Rule of Civil Procedure 23(a) and (b)(3) on behalf of a Class, consisting of all those who purchased or otherwise acquired Axsome common stock during the Class Period (the "Class"); and were damaged upon the revelation of the alleged corrective disclosures. Excluded from the Class are Defendants herein, the officers and directors of the Company, at all relevant times, members of their immediate

families and their legal representatives, heirs, successors or assigns and any entity in which Defendants have or had a controlling interest.

191. The members of the Class are so numerous that joinder of all members is impracticable. Throughout the Class Period, Axsome common stock was actively traded on the NASDAQ. While the exact number of Class members is unknown to Plaintiffs at this time and can be ascertained only through appropriate discovery, Plaintiffs believe that there are hundreds or thousands of members in the proposed Class. Record owners and other members of the Class may be identified from records maintained by Axsome or its transfer agent and may be notified of the pendency of this action by mail, using the form of notice similar to that customarily used in securities class actions.

192. Plaintiffs' claims are typical of the claims of the members of the Class as all members of the Class are similarly affected by Defendants' wrongful conduct in violation of federal law that is complained of herein.

193. Plaintiffs will fairly and adequately protect the interests of the members of the Class and have retained counsel competent and experienced in class and securities litigation. Plaintiffs have no interests antagonistic to or in conflict with those of the Class.

194. Common questions of law and fact exist as to all members of the Class and predominate over any questions solely affecting individual members of the Class. Among the questions of law and fact common to the Class are:

- whether Defendants' acts violated the federal securities laws as alleged herein;
- whether Defendants' statements to the investing public during the Class Period misrepresented material facts about the business, operations and management of Axsome related to the development of, and NDA for, AXS-07;
- whether the Individual Defendants caused Axsome to issue false and misleading statements during the Class Period;

- whether Defendants acted knowingly or recklessly in issuing false and misleading statements;

- whether the prices of Axsome common stock during the Class Period were artificially inflated because of the Defendants' conduct complained of herein; and

- whether the members of the Class have sustained damages and, if so, what is the proper measure of damages.

195. A class action is superior to all other available methods for the fair and efficient adjudication of this controversy since joinder of all members is impracticable. Furthermore, as the damages suffered by individual Class members may be relatively small, the expense and burden of individual litigation make it impossible for members of the Class to individually redress the wrongs done to them. There will be no difficulty in the management of this action as a class action.

X. APPLICABILITY OF PRESUMPTION OF RELIANCE: FRAUD-ON-THE-MARKET AND *AFFILIATED UTE* PRESUMPTIONS

196. Plaintiffs will rely, in part, upon the presumption of reliance established by the fraud-on-the-market doctrine in that:

- Defendants made public misrepresentations or failed to disclose material facts during the Class Period;

- the omissions and misrepresentations were material;

- Axsome common stock is traded in an efficient market;

- the Company's common stock was liquid and traded with moderate to heavy volume during the Class Period;

- the Company's common stock traded on the NASDAQ and was covered by multiple analysts during the Class Period;

- the misrepresentations and omissions alleged would tend to induce a reasonable investor to misjudge the value of the Company's common stock; and

- Plaintiffs and members of the Class purchased, acquired and/or sold Axsome common stock between the time the Defendants failed to disclose or misrepresented material facts and the time the true facts were disclosed, without knowledge of the omitted or misrepresented facts.

197. Based upon the foregoing, Plaintiffs and the members of the Class are entitled to a presumption of reliance upon the integrity of the market.

198. Alternatively, Plaintiffs and the members of the Class are entitled to the presumption of reliance established by the Supreme Court in *Affiliated Ute Citizens of the State of Utah v. United States*, 406 U.S. 128, 92 S. Ct. 2430 (1972), as Defendants omitted material information in their Class Period statements in violation of a duty to disclose such information, as detailed above.

XI. COUNT I

Violations of Section 10(b) of the Exchange Act and Rule 10b-5 Promulgated Thereunder Against Defendants Axsome, Tabuteau, Jacobson, and Laliberte

199. Plaintiffs repeat and re-allege each and every allegation contained above as if fully set forth herein.

200. This Count is asserted against Defendants and is based upon Section 10(b) of the Exchange Act, 15 U.S.C. § 78j(b), and Rule 10b-5 promulgated thereunder by the SEC.

201. During the Class Period, Defendants engaged in a plan, scheme, conspiracy and course of conduct, pursuant to which they knowingly or recklessly engaged in acts, transactions, practices and courses of business which operated as a fraud and deceit upon Plaintiffs and the other members of the Class; made various untrue statements of material facts and omitted to state material facts necessary in order to make the statements made, in light of the circumstances under which they were made, not misleading; and employed devices, schemes and artifices to defraud in connection with the purchase and sale of common stock. Such scheme was intended to, and, throughout the Class Period, did: (i) deceive the investing public, including Plaintiffs and other Class members, as alleged herein; (ii) artificially inflate and maintain the market price of Axsome's

common stock; and (iii) cause Plaintiffs and other members of the Class to purchase or otherwise acquire Axsome common stock at artificially inflated prices. In furtherance of this unlawful scheme, plan and course of conduct, Defendants, and each of them, took the actions set forth herein.

202. Pursuant to the above plan, scheme, conspiracy and course of conduct, each of the Defendants participated directly or indirectly in the preparation and/or issuance of the quarterly and annual reports, SEC filings, press releases and other statements and documents described above, including statements made to securities analysts and the media that were designed to influence the market for Axsome's common stock. Such reports, filings, releases and statements were materially false and misleading in that they failed to disclose material adverse information and misrepresented the truth about Axsome's finances and business prospects, including AXS-07.

203. By virtue of their positions at Axsome, Defendants had actual knowledge of the materially false and misleading statements and material omissions alleged herein and intended thereby to deceive Plaintiffs and the other members of the Class, or, in the alternative, Defendants acted with reckless disregard for the truth in that they failed or refused to ascertain and disclose such facts as would reveal the materially false and misleading nature of the statements made, although such facts were readily available to Defendants. Said acts and omissions of Defendants were committed willfully or with reckless disregard for the truth. In addition, each Defendant knew or recklessly disregarded that material facts were being misrepresented or omitted as described above.

204. Information showing that Defendants acted knowingly or with reckless disregard for the truth is peculiarly within Defendants' knowledge and control. As the senior managers

and/or directors of Axsome, the Individual Defendants had knowledge of the details of Axsome's internal affairs.

205. The Individual Defendants are liable both directly and indirectly for the wrongs complained of herein. Because of their positions of control and authority, the Individual Defendants were able to and did, directly or indirectly, control the content of the statements of Axsome. As officers and/or directors of a publicly-held company, the Individual Defendants had a duty to disseminate timely, accurate, and truthful information with respect to Axsome's businesses, operations, future financial condition and future prospects. As a result of the dissemination of the aforementioned false and misleading reports, releases and public statements, the market price of Axsome's common stock was artificially inflated throughout the Class Period. In ignorance of the adverse facts concerning Axsome's business and financial condition which were concealed by Defendants, Plaintiffs and the other members of the Class purchased or otherwise acquired Axsome's common stock at artificially inflated prices and relied upon the price of the securities, the integrity of the market for the securities and/or upon statements disseminated by Defendants, and were damaged thereby.

206. During the Class Period, Axsome's common stock was traded on an active and efficient market. Plaintiffs and the other members of the Class, relying on the materially false and misleading statements described herein, which the Defendants made, issued or caused to be disseminated, or relying upon the integrity of the market, purchased or otherwise acquired Axsome's common stock at prices artificially inflated by Defendants' wrongful conduct. Had Plaintiffs and the other members of the Class known the truth, they would not have purchased or otherwise acquired said common stock, or would not have purchased or otherwise acquired Axsome's common stock at the inflated prices that were paid. At the time of the purchases and/or

acquisitions by Plaintiffs and the Class, the true value of Axsome's common stock was substantially lower than the prices paid by Plaintiffs and the other members of the Class. The market price of Axsome's common stock declined sharply upon public disclosure of the facts alleged herein to the injury of Plaintiffs and Class members.

207. By reason of the conduct alleged herein, Defendants knowingly or recklessly, directly or indirectly, have violated Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder.

208. As a direct and proximate result of Defendants' wrongful conduct, Plaintiffs and the other members of the Class suffered damages in connection with their respective purchases, acquisitions and sales of the Company's common stock during the Class Period, upon the disclosure that the Company had been disseminating misrepresented statements to the investing public.

XII. COUNT II

Violations of Section 20(a) of the Exchange Act Against the Individual Defendants

209. Plaintiffs repeat and re-allege each and every allegation contained in the foregoing paragraphs as if fully set forth herein.

210. During the Class Period, the Individual Defendants participated in the operation and management of Axsome, and conducted and participated, directly and indirectly, in the conduct of Axsome's business affairs. Because of their senior positions, they knew the adverse non-public information about Axsome's statements described above.

211. As officers and/or directors of a publicly owned company, the Individual Defendants had a duty to disseminate accurate and truthful information with respect to Axsome's

financial condition and results of operations, and to correct promptly any public statements issued by Axsome which had become materially false or misleading.

212. Because of their positions of control and authority as senior officers, the Individual Defendants were able to, and did, control the contents of the various reports, press releases and public filings which Axsome disseminated in the marketplace during the Class Period concerning Axsome's results of operations. Throughout the Class Period, the Individual Defendants exercised their power and authority to cause Axsome to engage in the wrongful acts complained of herein. The Individual Defendants, therefore, were "controlling persons" of Axsome within the meaning of Section 20(a) of the Exchange Act. In this capacity, they participated in the unlawful conduct alleged which artificially inflated the market price of Axsome's common stock.

213. Each of the Individual Defendants, therefore, acted as a controlling person of Axsome. By reason of their senior management positions and/or being directors of Axsome, each of the Individual Defendants had the power to direct the actions of, and exercised the same to cause, Axsome to engage in the unlawful acts and conduct complained of herein. Each of the Individual Defendants exercised control over the general operations of Axsome and possessed the power to control the specific activities which comprise the primary violations about which Plaintiffs and the other members of the Class complain.

214. By reason of the above conduct, the Individual Defendants are liable pursuant to Section 20(a) of the Exchange Act for the violations committed by Axsome.

XIII. PRAYER FOR RELIEF

WHEREFORE, Plaintiffs demand judgment against Defendants as follows:

A. Determining that the instant action may be maintained as a class action under Rule 23 of the Federal Rules of Civil Procedure, and certifying Plaintiffs as the Class representatives;

B. Requiring Defendants to pay damages sustained by Plaintiffs and the Class by reason of the acts and transactions alleged herein;

C. Awarding Plaintiffs and the other members of the Class prejudgment and post-judgment interest, as well as their reasonable attorneys' fees, expert fees and other costs; and

D. Awarding such other and further relief as this Court may deem just and proper.

XIV. DEMAND FOR TRIAL BY JURY

Plaintiffs hereby demand a trial by jury.

Dated:

Respectfully submitted,

POMERANTZ LLP

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EXHIBIT 1

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SUMMARY

This mission critical, PDUFA, Pre-market, original surveillance inspection of a clinical trial sponsor, Axsome Therapeutics Inc. was conducted at the request of the office of Scientific Investigations/CDER. It was conducted in accordance with compliance program 7348.810, Sponsors, Contract Research Organizations and Monitors, and the assignment memorandum dated 5/4/2021 (**Attachment # 2)**. The inspection is part of the BIMO FY 21 workplan. The inspection was covered under eNSpect OPID # 200298 and FACTS # 12117778.

The assignment requested the inspection of Axsome Therapeutics Inc. and its conduct of two study protocols submitted under (b) (4)). This is the first FDA inspection for Axsome Therapeutics Inc. The protocols covered include:

(b) (4)

Records reviewed during this comprehensive inspection include but are not limited to organizational charts, study protocols, financial disclosures, form FDA 1572s, contracts/transfer of regulatory authority, standard operating procedures, monitoring reports, investigator CVs, investigator and monitor selection records, training records, IND annual reports, data collection and management records, case report forms, operational manuals, and test article accountability records.

A form FDA 483 "Inspectional Observation" was not issued at the conclusion of the current inspection. The following discussion items were presented and discussed with management during the close out meeting.

- Results and a copy of protocol # (b) (4) are not yet posted in clincaltrial.gov.
- Source records for protocol # (b) (4) were transcribed into paper Case Report Forms (CRFs) by site personnel. 100% of CRFs are not signed/initial and dated by the transcriber.
- Case report forms for three subjects enrolled in protocol # (b) (4) have data changes that were entered after the principal investigator signed and dated the CRFs.
- Two study monitors recruited and assigned monitoring duties for protocol # (b) (4) did not meet all requirements set forth in the sponsor's job descriptions for study monitors.
- The (b) (4) EDC data base system used to capture and maintain protocol # (b) (4) eCRFs does not have the capability to capture and maintain all eCRF audit trail history. For example, eCRFs audit history lacks information on the database lock date and by whom.

Each of the discussion items was discussed with management during the close-out meeting. Mr. Herriot (NMI) Tabuteau, Chief Executive Officer stated that the firm will not provide a written response to the FDA. Each discussion item is covered in detail in the **General Discussion with Management** section of this report.

There were no refusals and no samples were collected.

FACTS data and eNSpect data for the firm was reviewed and updated to reflect the firm's main line telephone number, fax number and e-mail address for the main point of contact.

ADMINISTRATIVE DATA

Inspected firm:	Axsome Therapeutics, Inc.
Location:	22 Cortlandt St Fl 16 New York, NY 10007-3139
Phone:	1-9212-332-3241
FAX:	1-212-320-0245
Mailing address:	22 Cortlandt St Fl 16 New York, NY 10007-3139
Email address:	(b) (6)
Dates of inspection:	6/21/2021-6/25/2021, 6/28/2021-7/1/2021
Days in the facility:	9
Participants:	**Geoffrey K Kilili, Investigator**

Non-FDA Participants: None

FMD-145 and post inspectional correspondence should be addressed to:
Herriot (NMI) Tabuteau, MD: Chief Executive Officer
Axsome Therapeutics Inc.,
22 Cortlandt St, 16th Floor,
New York, NY 10007
Phone: 212-203-5072
e-mail (b) (6)

This inspection was pre-announced. On 6/21/2021, I presented my credentials and issued a form FDA 482, "Notice of Inspection" to Herriot (NMI) Tabuteau, Chief Executive Officer, Axsome Therapeutics Inc. Dr. Tabuteau identified himself as the most responsible person. I explained the purpose of the inspection, and requested the documents needed to conduct the inspection. In addition to Dr. Tabuteau, the following individuals were present at the opening meeting:

- Shelly G. Ogiste: Senior director, quality.
- Caroline P. Streicher: Senior director, clinical operations.
- Amanda E. Jones: Senior vice president clinical development.
- Mark L. Jacobson: Chief operating officer.
- Cheryl A. Askew: Director, clinical operations.
- Kevin J. Laliberte: Executive vice president, product development.

HISTORY

Axsome Therapeutics Inc. is a biopharmaceutical company involved in the discovery and development of novel therapies for Central Nervous System (CNS) disorders. The company was founded in 2012 by Dr. Herriot (NMI) Tabuteau. Dr. Tabuteau is also the most responsible person and Chief Executive Officer (CEO). His office is located at 22 Cortlandt St Fl 16, New York, NY 10007. He explained the company does not currently have any subsidiaries.

During the opening meeting Ms. Amanda E. Jones Senior VP, clinical development, and Ms. Shelly G. Ogiste, Senior director, quality gave a presentation covering the history of Axsome Therapeutics Inc. its organizational structure and the clinical developmental of (b) (4) **(Exhibit GKK # 1).**

AXS-05 was granted FDA breakthrough therapy designation for the treatment of Major Depressive Disorder (MDD) disorder in 2019.

Currently, Axsome's pipeline of drug candidates include, AXS-05, indicated for major depressive disorder, alzheimer's disease agitation, and smoking sensation. AXS-07 for migraine. AXS-12 for narcolepsy, and AXS-14 for fibromyalgia.

Dr. Tabuteau explained that Axsome Therapeutics Inc. became a publicly traded company in 2015 and has approximately (b) (4) full time employees. This is the (b) (4) NDA submission for Axsome Therapeutics Inc.

The establishment's hours of operation are Monday to Friday (b) (4)

INTERSTATE (I.S.) COMMERCE AND JURISDICTION

Axsome Therapeutics Inc. is a sponsor of human based clinical research studies nationally. Shipping records show that the investigational product used during the conduct of protocol #(b) (4) (b) (4) was shipped from (b) (4) (currently known as (b) (4)) located at (b) (4) to a (b) (4) located at (b) (4) .

Shipping records show that the investigational product was shipped interstate from (b) (4) (b) (4) to clinical study sites located in various states in the US.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Herriot (NMI) Tabuteau MD, Chief Executive Officer: Dr. Tabuteau is the founder, Chief Executive officer and most responsible person in Axsome Therapeutics Inc. He stated that as the founder of Axsome Therapeutics Inc., he is and has been involve in almost every aspect associated with the development, implementation, and realization of (b) (4) drug development projects. These include but not limited to:

- Correspondence and interaction with FDA regulatory officials.
- Initial and continuing product development and regulatory strategies.
- Clinical development and clinical trial outlook and implementation.
- Protocol development and review.
- Budget and finance.
- IND and NDA fillings.
- Oversight all company departments and personnel.

Mr. Tabuteau was present and available throughout the duration of the inspection. He reports to the board of directors.

Ms. Amanda E. Jones, Senior VP, clinical development: Ms. Jones joined Axsome Therapeutics Inc. around June 2015 and assumed the position of VP, clinical development in 2020. She stated that her responsibilities include overseeing protocol development, statistical data analysis, writing and review of clinical study reports, and third party vendor qualification and management.

Ms. Jones was one of the key points of conduct during the inspection and provided me with the records I needed to complete the inspection and provided answers/clarification to my questions. She reports to Dr. Herriot (NMI) Tabuteau, Chief Executive Officer.

Shelly G. Ogiste, Senior Director, quality: Ms. Ogiste joined Axsome Therapeutics Inc. in January 2020. She is the first employee of the quality assurance unit at the Axsome Therapeutics Inc. and tasked with the responsibilities of overseeing the establishment of an internal quality assurance unit. She stated that her other responsibilities include overseeing GMP and GCP quality assurance training, qualification of third party vendors, site audits, SOP development and management systems, and oversight on site monitoring policies and practices.

Ms. Ogiste was another key point of contact during the inspection. She accompanied me every day of the inspection, provided answers/clarification to my inquiries and managed my day to day requests during the inspection. She reports to Kevin J. Laliberte, Executive VP, Product strategy.

Caroline P. Streicher, Senior Director Clinical Operations: Ms. Streicher joined Axsome Therapeutics Inc. in 2019. She stated that her responsibilities include development and review of study documents including the protocol, study monitoring plans and safety monitoring plans. She also oversees the selection of site/principal investigators and management of the clinical trial team. Ms. Streicher, accompanied me every day of the inspection, provided answers/clarification to my inquiries and managed my day to day requests during the inspection.

Cheryl A. Askew, Director Clinical Operations: Ms. Askew joined Axsome Therapeutics Inc. in September 2018. She stated that her responsibilities include management of study monitoring activities, selection and workload management for field clinical research associates, and if necessary, participate in escalation/resolution of site action items. Ms. Askew served the role of scribe during the inspection. She reports to Ms. Amanda E. Jones senior VP, clinical development.

Cedric J. O'Gorman, MD, Senior VP Medial affairs: Dr. O'Gorman joined Axsome Therapeutics Inc. in September 2017. He stated that his responsibilities include overseeing and providing medical monitoring services, safety meetings, and evaluation of adverse events and adverse event reports. Mr. O'Gorman provided me with information and clarifications appertaining to the procedures used in the capture and reporting of adverse events during the conduct of both protocol # (b) (4) (b) (4) (b) (4) He reports to Dr. Herriot (NMI) Tabuteau, Chief Executive Officer.

Kevin J. Laliberte, Executive VP Product strategy: Mr. Laliberte joined Axsome Therapeutics Inc. in January 2021. He stated that he previously worked (b) (6) (b) (6) . He stated that his responsibilities include overseeing multiple departments

including regulatory, chemistry manufacturing and controls, pharmacovigilance, supply chain, medical affairs, and research and operations. He reports to Dr. Herriot (NMI) Tabuteau, CEO.

(b) (6) (b) (6) **Senior clinical trial manager:** Ms. (b) (6) stated that she acted as a clinical trial manager and clinical site monitor during the conduct of both protocol # (b) (4) (b) (4)(b) (4) Ms. (b) (6) provided me with details and clarifications appertaining to the site monitoring activities during the conduct of protocol # (b) (4) (b) (4) She reports to Ms. Amanda E. Jones, senior VP, clinical development.

ORGANIZATION AND PERSONNEL

During the opening meeting, Ms. Jones and Ms. Ogiste provided a presentation focused on the branches and individuals involved in the development and conduct of protocol # (b) (4) and # (b) (4) **(Exhibit GKK # 1**). Dr. Herriot (NMI) Tabuteau is the CEO of Axsome Therapeutics Inc. and the most responsible person. He has oversight over the following five key product development departments:

- Quality assurance/product strategy, headed by executive VP, Kevin J. Laliberte.
- Operations, headed by the chief operational officer, Mark L. Jacobson.
- Clinical development, headed by senior VP, Ms. Amanda E. Jones.
- Finance, headed by the chief financial officer Nick X. Pizzle.
- Commercial, headed by Lori A. Englebert, Executive VP, commerce, and business development.

Ms. Jones stated that she has the authority to review and approve study reports and data listings for both protocol # (b) (4)

Ms. Jones explained that Cedric J. O'Gorman, Senior VP medial affairs is the chief medical monitor and was responsible for making final evaluations and decisions in the review of adverse events and safety information for both protocol # (b) (4) (b) (4)

For both protocol # (b) (4) (b) (4) clinical supplies including management and oversight of third party contractors was overseen by Chemistry, Manufacturing and Control (CMC) team. Ms. Jones stated that key individuals included Karen L. TenHuisen, VP CMC, and (b) (6) (b) (6) associate manager, research, and operations. Both Ms. TenHuisen and Mr. (b) (6) reports to Kevin J. Laliberte, executive VP product strategy.

Protocol # ((b) (4) Ms. Jones stated that the initial protocol draft was developed by Kellie A. Kennon, director clinical operations and (b) (6) (b) (6) trial manager. The final draft was signed and approved by Cedric J. O'Gorman, medical monitor and senior VP medical affairs, Robert Niecestro VP clinical and regulatory affairs and Kellie A. Kennon.

Ms. Jones stated that implementation of the study clinical trial events including investigator qualification/selection, selection of study monitors, monitoring activities and review of monitoring reports were overseen by Ms. Kennon, and Ms. (b) (6) Both Ms. Kennon and Ms. (b) (6) reports to Ms. Amanda E. Jones Senior VP, clinical development.

I obtained copies of agreements documenting the responsibilities transferred to third party contractors. I observed some contractors were reported on form 1571 that was submitted to the FDA. These include, (b) (4) .

CRO name	Address	Responsibilities transferred	Exhibit
(b) (4)	(b) (4)	(b) (4)	GKK # 2
			GKK # 3
			GKK # 4
			GKK # 5
			GKK # 6
			GKK # 7

Protocol # (b) (4) Ms. Caroline P. Streicher, senior director clinical operations stated that protocol development was done by Amanda Jones, senior VP, clinical development, and Cedric J. O'Gorman, senior VP medial affairs. Ms. Streicher and (b) (6) (b) (6) senior clinical trial manager provided feedback. The final protocol was approved by Ms. Jones and Mr. O'Gorman.

Ms. Streicher explained that she was the key individual involved in study site administration including qualification and selection of clinical investigators. Cheryl A. Askew, director clinical operation and (b) (6) (b) (6) senior clinical trial manager completed monitor selection and implementation of monitoring activities. They report to Ms. Jones, senior VP, clinical development.

I obtained a list of third party contractors **(Exhibit GKK # 8).** I observed that form FDA 1571 for protocol # (b) (4) did not list any of the third party contractors. Vendors with signed work transfer agreements include the following:

CRO name	Address	Responsibilities transferred	Exhibit
(b) (4)	(b) (4)	(b) (4)	GKK # 4
			GKK # 9
			GKK # 10
			GKK # 11
			GKK # 12
			GKK # 13
			GKK # 14
			GKK # 15

REGISTRATION OF STUDIES ON CLINICALTRIAL.GOV

Protocol # (b) (4) Initial registration of the study on clinicaltrials.gov occurred on (b) (4) under clinicaltrials.gov identifier #(b) (4). The first subject was enrolled on (b) (4). The date of the last visit for the final study subject (visit 9) occurred on 12/27/2018.

My review of the current status of protocol # (b) (4) in clincaltrial.gov indicated that a summary of study results and a copy of the protocol have not yet been posted in clincaltrial.gov per regulatory requirements. Please see the **"General Discussion with Management"** section of this report for details.

Protocol # (b) (4) Initial registration of the study on clinicaltrials.gov occurred on (b) (4) under clinicaltrials.gov identifier # (b) (4). The first subject was enrolled on (b) (4). The primary completion date of the study is (b) (4).

My review of the current status of protocol # (b) (4) in clincaltrial.gov indicated that a summary of study results and a copy of the study protocol have not been posted in clincaltrial.gov per regulatory requirements.

Ms. Jones explained that the sponsor received FDA approval to delay the posting for one year until 2022 **(Exhibit GKK # 16).**

For both protocol # (b) (4) and protocol # (b) (4) I reviewed and determined that the sponsor completed and submitted form FDA 3674 to the FDA. I also reviewed master informed consent documents that the sponsor distributed to clinical sites and determined that the required statement referencing clinicaltrial.gov was included.

SELECTION AND MONITORING OF CLINICAL INVESTIGATORS

All study site participating in the conduct of protocol # (b) (4) and protocol # (b) (4) were located in the US.

For protocol # (b) (4) four sites were activated and enrolled subjects. I reviewed records for all four sites. I confirmed that all four investigators had a signed form FDA 1572.

Forty three sites were activated for protocol # (b) (4) Three sites including 841, 820 and 825 did not enroll any subjects. Ms. Jones stated that all 43 clinical investigators signed form FDA 1572 before participation in the clinical study. I selected twelve sites with high subject enrollment for review including the sites identified in the assignment memo. These sites include 806, 807, 808, 811, 812, 814, 817, 823, 828, 830, 833, and 834. I confirmed that all twelve investigators had a signed form FDA 1572.

The following paragraphs contain information covering both protocol # (b) (4) *and #* (b) (4) *unless otherwise indicated.*

I reviewed the sponsor's SOPs for site evaluation and investigator selection and found no concerns. Ms. Jones and Ms. Streicher explained that key considerations for the selection of investigators included the completion of a feasibility questionnaire, a current CV, valid medical license, experience in (b) (4), previous experience working with the investigator as well as regulatory and debarment actions. I reviewed these records and found that the sponsor followed the SOP requirements and the clinical investigators were qualified by education and experience.

I reviewed site selection and activations letters documenting that the sponsor provided investigators with a start-up package containing necessary information such as the protocol, investigator brochure, and regulatory document completion guidelines prior to initiation of the clinical trial. I also reviewed site initiation reports and PowerPoint slides that the sponsor used to conduct site initiation training for participating sites. My review of these records did not reveal any concerns.

I observed that the sponsor criteria for dealing with non-compliant investigators was included in the clinical monitoring plans for both protocol # (b) (4) and # (b) (4) Ms. Jones and Ms. Streicher explained that, generally, non-compliant incidences and applicable corrective action plans are discussed with the affected investigator during site monitoring visits. They added that, if the site fails to resolve the matter in a timely manner, the issue can be escalated to the study lead and upper management.

My review of site monitoring reports and statements from Ms. Jones and Ms. Streicher indicated that all investigators remained compliant during the conduct of protocol # (b) (4) and # (b) (4) No incidences of escalation to management occurred and no sites were terminated.

SELECTION OF MONITORS

I obtained a list of all Clinical Research Associates (CRA) that were assigned study monitoring duties during the conduct of protocol # (b) (4) and # (b) (4) I also obtained a copy of their CVs and job descriptions.

Per the job descriptions **(Exhibit GKK # 17),** CRA qualifications required BA/BS or equivalent degree in a scientific field and a minimum of three years of clinical trial experience.

My review of monitoring reports and CVs showed that CRAs (b) (6) participated in the monitoring of protocol # (b) (4) but did not meet the experience and /or the education requirements. Please see the **"General Discussion with Management"** section of this report for details.

Ms. Jones explained that CRAs ensured that study sites remained compliant to the protocol and applicable regulations. Medical monitors and medical monitoring involved medical/scientific consultation and providing guidance/support to the study sites regarding, but not limited to, patient eligibility, safety questions, and study-specific safety training. Please see the "**Safety/ Adverse Event Reporting"** section of this report for more details on safety monitoring and reporting.

MONITORING PROCEDURES AND ACTIVITIES

Protocol # (b) (4) Sponsor monitoring procedures are documented in the clinical monitoring plan **(Exhibit GKK # 18).** I reviewed monitoring reports for all four sites that participated in the conduct of protocol # (b) (4) I observed that the monitoring reports were reviewed and signed by either Kellie Kennon, director clinical operations or (b) (6) (b) (6) associate clinical trial manager.

Protocol # (b) (4) The sponsor monitoring procedures used during the conduct of protocol # (b) (4) are documented in the clinical monitoring plan **(Exhibit GKK # 19).** I reviewed monitoring reports for the twelve sites identified above that participated in the conduct of protocol # (b) (4) I observed that monitoring reports were reviewed and signed by either (b) (6) (b) (6) senior clinical trial manager or Caroline P. Streicher: senior director, clinical operations.

The following paragraphs contain information covering both protocol # (b) (4) *and #* (b) (4) *unless otherwise indicated.*

For both protocol # (b) (4) and # (b) (4) I reviewed site evaluation reports, initiation visit reports and interim monitoring visit reports and found them to reflect that investigators were compliant to required regulations, and SOPs. I found that the sponsor's monitoring activities were adequate and in line with the procedures described in the study monitoring plans and applicable SOPs. I did not observe any concerns.

I observed that each monitoring report included sections covering the evaluation and documentation of the adequacy of the investigator oversight, whether the investigator and site staff maintained compliance to the protocol and applicable regulations including IRB approvals. Other areas covered include, obtaining of informed consent, IP accountability and reconciliations, as well as adequacy of the site facilities and equipment. Monitoring reports also have sections documenting if study sites properly documented and reported adverse events and any incidents of protocol deviation.

I observed that monitoring reports also captured and tracked any observed discrepancies, queries or action items and the implementation of any agreed upon corrective actions. Based on the time frames documented in monitoring reports, it appeared that all sites moved to resolve any existing action items and queries in a timely manner. I did not observe any concerns.

Based on the study monitoring plans and statements from Ms. Jones and Ms. Streicher, Source Document Verification (SDV) against corresponding CRFs occurred for 100 % of source documents with the exception of subject diaries ((b) (4)). Random sampling was used for the verification of (b) (4).

Ms. (b) (6) explained that CRAs are required to document subject IDs and the nature of source records verified at each monitoring visit. She added that the firm did not use any data verification forms. My review of monitoring visit reports confirmed that this was the case.

Ms. (b) (6) stated that only delegated study site personnel have the authority to make corrections to CRFs. Any discrepancies observed during monitoring were resolved onsite or a query was presentation to the affected sites to review and update/correct as necessary.

QUALITY ASSURANCE

Ms. Jones and Ms. Ogiste, senior director, quality, explained that Axsome Therapeutics Inc. did not have a dedicated quality assurance unit during the conduct of protocol # (b) (4) or protocol # (b) (4) She stated that the firm relied on standard operating procedures and independent contractors to oversee the implementation of necessary QA functions and audits. For example, **Exhibit GKK #1, Page 22.**

Ms. Ogiste explained that QA auditors maintain oversight over the quality of many of the processes involved in the conduct of a clinical trial including Good Manufacturing Procedures, Good Clinical Procedures and the quality of site monitoring processes and procedures.

She stated that two sites, 807 and 814 both participating in the conduct of protocol # (b) (4) were audited and reported in the Clinical Study Report submitted to the FDA. None of the site participating in the conduct of protocol # (b) (4) were audited.

SAFETY ADVERSE EVENTS REPORTING

The procedures used by the sponsor to govern receiving, processing, evaluation and monitoring of safety information/unanticipated adverse events are detailed in the following documents:

- Protocol # (b) (4) safety management plan (**Exhibit GKK # 21).**
- Protocol # (b) (4) safety management plan (**Exhibit GKK # 22).**

Cedric J. O'Gorman, MD, senior VP medial affairs was responsible for the final evaluations and decisions in the review of adverse events and safety information during the conduct of both protocol # (b) (4) and # (b) (4) He stated that Axsome Therapeutics Inc. contracted (b) (4) to provide pharmacovigilance (PV) services for both protocols.

My review of the safety management plan and statements from Dr. O'Gorman showed that study sites were required to report all SAEs to (b) (4) regardless of causality and expectedness. (b) (4) was responsible for the initial review, triage, SAE database entry, Medwatch safety report preparation and submission to the sponsor.

Axsome responsibilities included review of the SAE reports for medical accuracy and either concur or request modifications of the reported causality, expectedness, and regulatory reportability. Axsome was also responsible for the reporting of qualified SAEs to the FDA, the IRB, and clinical investigators.

Dr. O'Gorman stated that he engaged with investigators when necessary to provided medical opinion and answer any questions appertaining to (b) (4) drug interactions, drug safety and concomitant medications. He added that investigators were trained and advised to capture and report to the sponsor all adverse events that are observed or reported by the patient during study visits.

He explained that safety meetings were held each quarter to review safety data and analyze the rate, frequency, and severity of adverse events for potential trends and concerns. I reviewed a copy of the formal safety meeting report and found no concerns.

Dr. O'Gorman stated that for both protocol # (b) (4) and # (b) (4) there were no SAEs or adverse events that met the regulatory reporting criteria for SUSARS or Adverse Events of Special Interest (AESI). There were no IND safety reports that required submission to clinical investigators or the FDA.

My review of SAE reports showed there was one SAE report associated with protocol # (b) (4) One subject claimed to have experienced an episode of psychosis that led to overnight hospitalization. Since the hospitalization was for less than 24 hours, the sponsor requested the SAE to be downgraded to an AE. Information associated with the SAE report and its down grade is included as **Exhibit GKK # 23.**

One SAE of pancreatitis was reported for protocol # (b) (4) The investigator documentation indicated that the SAE was not related to the study drug. Dr. O'Gorman and Ms. Streicher stated that the SAE did not meet the regulatory reporting criteria for SUSAR or AESI.

For the four sites (protocol # (b) (4) and twelve sites (protocol # (b) (4) selected for review, I performed a random comparison of the nature, relationship, severity, intensity, and/or expectedness of adverse events reported in subject case report forms to those reported in the assignment data listings and found no discrepancies.

I did not find any evidence to suggest any under documentation or reporting of AEs. Dr. O'Gorman and Ms. Jones stated that all known AEs associated with (b) (4) (b) (4) in plasma in both animals and human was included in the investigational brochure provided to clinical investigators (**Exhibit GKK # 20).**

DATA COLLECTION AND HANDLING

Ms. Jones provided a copy listing all clinical studies included in the clinical study report for NDA (b) (4)(**Exhibit GKK # 24).** I observed that both protocol # (b) (4) and protocol # (b) (4) were included in the list.

Ms. Jones stated that a data safety monitoring board was not constituted for either protocol # (b) (4) or protocol # (b) (4) She explained that it is the sponsors' position that (b) (4) are already marketed as individual agents and their safety profiles are well known and documented.

Protocol # (b) (4) ***data collection and handling***

I obtained a copy of the clinical study report the sponsor submitted with the NDA application. I verified that clinical investigators for all four sites that signed form FDA 1572 to participate in the conduct of protocol # (b) (4) were included. I did not observe any discrepancies.

I obtained a list documenting all participating study sites and the number of subjects enrolled at each site. I confirmed that the total number of randomized subjects matched the number indicated in the assignment memo and data listings. I verified that subject disposition and randomization data documented in the assignment data listings matched with data documented in the enrollment logs and CRFs submitted to the sponsor for the four sites. I did not observe any discrepancies.

I obtained and reviewed a copy of the sponsor clinical data management plan identifying individual stakeholders, their responsibilities, and the data management procedures followed during the conduct of Protocol # (b) (4) **(Exhibit GKK # 25).**

Ms. (b) (6) explained source data was transcribed into paper Case Report Forms (CRFs) by site personnel. I observed that 100% of the transcribed CRFs were not signed or initialed and dated by the individuals completing the transactions. Please see the **"General Discussion with Management"** section of this report for details.

CRFs were verified against source documents by study monitors during site monitoring visits. Each completed CRF casebook was signed by the principal investigator to acknowledge that the CRFs are complete and accurate.

During my review of completed and signed CRFs, I observed that CRFs for three subjects had data changes that were entered after the date of the principal investigator's confirmatory signature. Please see the **"General Discussion with Management"** section of this report for details.

I verified that subject disposition, adverse events, primary endpoint efficacy data, and concomitant medication data documented in the paper case reports forms matched with corresponding data provided in the assignment data listings for sites (b) (7)(E). I did not observe any discrepancies.

Paper CRFs were collected from study sites by study monitors and mailed to the sponsor address accompanied by a signed CRF transmittal log. A designated Axsome Therapeutics Inc. official signed each CRF transmittal log to confirm receipt. I performed a random review of CRF transmittal forms and found no concerns.

Ms. Jones stated that (b) (4)., **(Exhibit GKK # 5)** was contracted to design, a secure database equipped with audit trail capabilities. I reviewed user acceptance testing, and validation reports indicating that the software met the required release specifications before implementation.

Ms. Jones explained that two copies of the database were set up to enable double data entry and automated verification. Data captured in paper CRFs was transcribed into the Ofni electronic database by designated sponsor personnel. A data comparison software (b) (4) " was used to compare data entries between the two databases to identify inconsistences and generate queries. Data Clarification Forms (DCF) were submitted to the affected study sites for clarifications. The principal investigator signed each DCF and returned to the sponsor. I reviewed randomly selected DCFs and found no concerns.

Once all queries were resolved and the data deemed accurate, the data base was locked on 12/28/2018 and study unblinding procedures were implemented.

Protocol # (b) (4) ***Randomization and Blinding Procedures***

Ms. Jones stated that Axsome Therapeutics Inc. contracted (b) (4) ., **(Exhibit GKK # 6)** and (b) (4) **(Exhibit GKK # 4)** to provide randomization and blinding services per protocol specifications. She explained that randomization schedule was generated by an independent unblinded statistician at (b) (4) . and provided to an unblinded clinical supply manager at (b) (4) .

Per Ms. (b) (6) statement and my review of the work agreement, blinding of the Investigational Product (IP) at (b) (4) occurred as follows:

- (b) (4) prepared treatment (b) (4) (b) (4) packaged into temper-evident sealed carton.
- Each (b) (4) was identified with the same unique med #.
- Med #s were merged with the randomized schedule to create a randomized kit list.
- Clinical investigator sites were provided with a randomization number list linked to a kit med #.
- Randomization numbers were assigned sequentially at the randomization visit.
- Subjects were dispensed the IP bottle identified with the med # number linked to their randomization number.

Jones stated that there were no accidental or planned unblinding incidences throughout the conduct of the study.

I reviewed records documenting sign off by the responsible parties conforming that all prerequisites for study unblinding including data base lock occurred on 12/28/2018.

I performed an unblinded review of the IP med #s dispensed to subjects at the two sites identified in the assignment memo, (b) (7)(E)) and performed a random comparison with the subject treatment assignment allocations indicated in the assignment data listings and found no discrepancies.

Protocol # (b) (4) ***data collection and handling***

I obtained a copy of the clinical study report the sponsor submitted to the FDA. I verified that all forty three investigators who signed form FDA 1572 were listed in the clinical study report included with the NDA marketing application. I did not observe any discrepancies.

I obtained a list documenting all participating study sites and the number of subjects enrolled at each site. I confirmed that the total number of randomized subjects for all sites matched the number indicated in the assignment memo. For the twelve sites selected for review, I confirmed that the number of randomized subjects indicated for each site matched with the number documented in the site enrollment logs.

For the three sites identified in the assignment memo (b) (7)(E)), I verified that subject disposition and randomization data documented in the assignment data listings matched with the

data documented in the enrollment logs and CRFs submitted to the sponsor. I did not observe any discrepancies.

Case report forms for this study were maintained in electronic format using (b) (4) (b) (4) Electronic Data Capture (EDC) system. I reviewed user acceptance and validation records documenting that the system was tested and passed validation for its intended use prior to the database "(b) (4)" date.

(b) (4) . **(Exhibit GKK # 13)**, through its affiliate (b) (4) was contracted to perform data management services after data base "(b) (4)" per the applicable data management plans and/or SOPs. I obtained and reviewed a copy of the sponsor clinical data management plan describing roles and responsibilities involved in data management, data flow, collection, and validation during the conduct of protocol # (b) (4) **(Exhibit GKK # 26).**

Ms. Jones explained that a designated study site personnel transcribed data captured in source documents into the EDC eCRF system. Source data verification was performed at monitoring visits. Additional data review and cleaning including query generation and resolution was performed by the Data Management (DM) team. Once the data was deemed accurate, the Principal Investigator (PI) signed off on each eCRF casebook. At this point, the eCRF is soft locked for further entry or edits.

I reviewed the EDC audit trail history and observed that the system captured user IDs, date/time of data entry, data changes, monitor source data verification events as well as DM data review and PI sign off events. I however, observed that each eCRF audit history did not capture audit trail data associated with when the data base was locked or when PI signature is invalidated when updates or edits are applied to an already PI signed/soft locked eCRF. Please see the **"General Discussion with Management"** section of this report for details.

I reviewed records documenting that all pre-data base lock requirements were completed and required approvals obtained before the data base was locked on 12/5/2019.

Ms. Jones explained that, the final raw datasets and the relevant data management documents are filed in Axsome's (b) (4). Axsome (b) (4) is hosted by (b) (4) User access to the Axsome (b) (4) account requires approval by Ms. Jones and unique login in credentials.

I verified that subject disposition, adverse events, primary endpoint efficacy data, and concomitant medication data documented in the eCRFs matched with corresponding data provided in the assignment data listings for sites (b) (7)(E) . I did not observe any discrepancies.

Protocol # (b) (4) ***Randomization and Blinding Procedures***

Ms. Jones stated that to protect blinding, there was only two authorized unblinded individuals, (b) (4) (b) (4)) and (b) (4)). Ms. Jones explained that Ms. (b) (4) generated the required randomization sequence list per protocol specifications and e-mailed a password protected copy to Ms (b) (4).

(b) (4) was contracted to prepare (b) (4) (b) (4) **(Exhibit GKK # 10).** Each (b) (4) was coded using a unique med # and linked to the randomized sequence list creating the final coded randomized sequence list. This was provided back to Ms. (b) (4) for verification. I reviewed e-mail correspondence between Ms. (b) (4) and Ms. (b) (4) and found no concerns.

The study used (b) (4) EDC IWRS system to perform subject randomization. At the randomization visit, the system assigned each subject a randomization number linking the subject to an assigned treatment allocation. At dosing visits, a pharmacist would input the required subject credentials and the system provided a printout documenting the med # to be dispensed to the subject.

I selected a random sample of subjects from sites (b) (7)(E) and verified that the med #s dispensed to the subjects identified with the treatment assignment for each subject in the source randomization schedule. I also verified that randomization data provided in the data listings matched with that documented in the source randomization schedule. I did not observe any discrepancies.

Ms. Jones stated that there were no accidental or planned unblinding incidences throughout the conduct of the study. My review of the sponsor records did not reveal evidence to suggest otherwise.

RECORD RETENTION
No objectionable items were observed with respect to record retention during the inspection.

FINANCIAL DISCLOSURE
I reviewed financial disclosure records and found that the sponsor obtained and reported to the FDA financial disclosures from all principal investigators. None of the principal investigators participating in protocol # (b) (4) or # (b) (4) reported a financial conflict of interest.

I also confirmed that the sponsor collected financial disclosures for all sub-investigators documented in forms FDA 1572. I did not observe any discrepancies.

ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES
(b) (4) This is a commercial secure platform for organizing and sharing of confidential documents. Ms. Jones explained that Axsome used (b) (4) to stored/archive all clinical documents for both protocol # (b) (4) and # (b) (4) including the eTMFs. Ms. Jones is the manager and has the authority to grant access to the Axsome (b) (4) account. Unique log in credential are required for access.

Clinical trial management system (CTMS): Ms. Streicher, Senior director, clinical operations, explained that the commercial CTMS system used by Axsome was developed and managed by (b) (4) She added that Axsome used the CTMS to perform clinical trial monitoring functions including report writing, review and approval for both protocol # (b) (4) and # (b) (4) Completed monitoring reports are downloaded and uploaded to (b) (4)

(b) (4) : This was a custom developed software for Axsome by (b) (4) **(Exhibit GKK # 5)**. It was used to enable transcription of protocol # (b) (4) paper CRFs into electronic documents. Ms. Jones sated that the finalized paper CRFs were electronically scanned and uploaded into (b) (4)

(b) (4) *Electronic Data Capture (EDC) system*: This is a commercial data management software developed by (b) (4) . It is the EDC system used to capture electronic CRFs, subject randomization, tracking randomization and drug dispensing during the conduct of protocol # (b) (4) Ms. Streicher explained that user access requests and approval was managed through the (b) (4) web based portal.

Application of relevant electronic systems for data collection and handling, user acceptance testing/validation, audit trail and security capabilities are further described in the **Data Collection and Handling** section of this report.

I did not observe any objectionable items related to the procedures in place for setup, user authorization, training, security or data back-up and recovery procedure.

TEST ARTICLE

Axsome Therapeutics Inc. contracted (b) (4) to manufacture the investigational product, (b) (4) used in the conduct of both protocol # (b) (4) and # (b) (4) (b) (4) (b) (4), was contracted to provide blinding, labelling, packaging, storage, and shipping services.

I obtained and reviewed certificate of analysis records documenting that the IP used in the conduct of protocol # (b) (4) and # (b) (4) met the required release specifications.

For protocol # (b) (4) manufacturer lot numbers analyzed/certified include (b) (4) and (b) (4) (Active drug (b) (4)) and (b) (4)

For protocol # (b) (4) manufacturer lot numbers analyzed/certified include, (b) (4) (Active drug (b) (4)) and (b) (4)).

Shipping records show that the IP was shipped from (b) (4) to (b) (4) in (b) (4) where labeling, blinded coding and packaging into treatment kits was performed. Completed treatment kits were then shipped to a (b) (4) located at (b) (4) , (b) (4) under controlled room temperature.

The (b) (4) served as the storage facility and dispatch point for IP shipping to study sites during the conduct of both protocol # (b) (4) and # (b) (4)

The investigational brochure states that (b) (4) should be stored at temperatures not exceeding (b) (4). Statements from Ms. Jones and my review of storage facility memos indicated that the storage

facility unit was maintained at 20° C +/- 5° C. I reviewed temperature charts documenting minimum and maximum temperatures during shipping from (b) (4) to (b) (4), and at the storage facility during the conduct of # protocol # (b) (4) and # (b) (4) and found no concerns.

My review of depot to study site shipping records for both protocol # (b) (4) and # (b) (4) showed that shipping occurred overnight at room temperature. I reviewed records documenting that upon receipt, sites inspected, acknowledged, and reported to the sponsor that the IP was received in good condition.

I obtained and reviewed records documenting names and addresses of clinical investigators that the IP was shipped to. I observed that the records documented dates, quantity, and code marks associated with each shipment. I did not observe any concerns.

I reviewed packing slips, site receiving records, dispensing and unused drug return records for all four sites (protocol # (b) (4) and the twelve sites selected for review (protocol # (b) (4) I found that the sponsors records were sufficient to reconstruct and reconcile IP usage at the study sites. I did not observe any concerns.

Ms. Jones stated that none of the IP was recalled, withdrawn, or returned for any reason during the conduct of either protocol # (b) (4) or # (b) (4) My review of IP records did not reveal any evidence to suggest otherwise.

No objectionable items were observed with regard to labeling of the test article.

DEVICES
This is not a device study and therefore this section is not applicable to this inspection and report.

EMERGENCY RESEARCH
Ms. Jones stated that there was no emergency research use of (b) (4)

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE
No objectionable items were observed and no form FDA 483, "Inspectional Observations", was issued during this inspection.

REFUSALS
No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT
The following five discussion items were presented to the management at the close out meeting held on 7/1/2021 and attended by:

- Herriot (NMI) Tabuteau: Chief Executive Officer
- Shelly G. Ogiste: Senior director, quality.
- Caroline P. Streicher: Senior director, clinical operations.

- Amanda E. Jones: Senior vice president clinical development.
- Mark L. Jacobson: Chief operating officer.
- Cheryl A. Askew: Director, clinical operations.
- Kevin J. Laliberte: Executive vice president, product development

1. *Results and a copy of protocol #(b) (4) are not yet posted in clincaltrial.gov*
My review of the current status of protocol #(b) (4) in clincaltrial.gov indicated that a summary of study results and a copy of the protocol have not yet been posted in clincaltrial.gov at the time of the current inspection **(Exhibit GKK # 27, Page 1 – 6).** Study case report forms show it has been over 2.5 years since the date of the last visit for the final study subject (visit 9) which occurred on 12/27/2018 **(Exhibit GKK # 27, Page 7 – 8).**

   Ms. Jones explained that the sponsor submitted a request for extension to the FDA around 3/18/2021. FDA declined to approve the request stating that the information provided does not appear sufficient to evaluate whether there is good cause for an extension **(Exhibit GKK # 27, page 9 – 10).** She stated that the required document preparations are complete, and the required data will be posted in clinicaltrial.gov within 1 – 2 months period.

2. *100% of CRFs of the CRFs are not signed or initial and dated by the author.*
Source records for protocol #(b) (4) were transcribed into paper Case Report Forms (CRFs) by site personnel. I observed that for all four study sites, 100% of the transcribed CRFs were not signed or initiated and dated by the individual completing the transcription. For example, **Exhibit GKK # 28.**

   Dr. Tabuteau acknowledged the oversight and indicated that mitigating corrective action will be implemented going forward.

3. *Case report forms for three subjects enrolled in protocol #(b) (4) have data changes that were entered after the principal investigator signed and dated the CRFs as follows.*

- Subject (b) (6) Casebook was signed by the PI on 10/17/2018. Data changes on page 43 "(b) (4) scores" are dated 10/18/2018 (**Exhibit GKK # 29, Page 1 – 2**).

- Subjec (b) (6) : Casebook was signed by the PI on 10/18/2018. Data changes on page 19 "Study drug dispensation" are dated 11/30/2018 (**Exhibit GKK # 29, Page 3 – 4**).

- Subject (b) (6): Casebook was signed by the PI on 9/25/2018. Data changes on page 3 "Medical and psychiatric history" are dated 9/26/2018 (**Exhibit GKK # 29, Page 5 – 6**).

   Dr. Tabuteau acknowledged the oversight and indicated that mitigating corrective action will be implemented going forward.

4. *Two study monitors recruited and assigned monitoring duties for protocol #(b) (4) did not have a college degree and/ or 3 years of experience per the requirements set forth in the sponsor's job descriptions for study monitors **(Exhibit GKK # 17)**.*

- Per (b) (6) CV, he became a clinical trial assistant on 7/2018 and a research associates in August of 2019 (**Exhibit GKK # 30, Page 1**). Monitoring reports show that he conducted monitoring activities and wrote monitoring reports on 11/13/2019 for site (b) (7)(E) (**Exhibit GKK # 30, Page 2 – 8)** and on 10/24/2019 and site 807 (**Exhibit GKK # 30, Page 9 – 19).**

- (b) (6) CV indicates the highest level of education attained is high school (**Exhibit GKK # 31, Page 8)**. Monitoring reports show that he conducted monitoring activities and wrote monitoring reports for site (b) (7)(E) in numerous occasions (**Exhibit GKK # 31, Page 9 – 14).**

  Dr. Tabuteau acknowledged the oversight and indicated that mitigating corrective action will be implemented going forward.

5. *The (b) (4) EDC database system used to capture and maintain protocol #* (b) (4) *eCRFs does not have the capability to capture and maintain all eCRF audit trail history.*

- For example, eCRFs audit history lacks information on the database lock date/time and by whom **(Exhibit GKK # 32, Page 1 – 2).** Ms. Jones stated that the EDC system captured audit history data reflecting when locking procedures were applied to the full study database **(Exhibit GKK # 32, Page 3).** This data is not captured in individual subject casebooks.

- eCRF audit history did not capture data associated with PI signature invalidation when updates or edits are applied to an already signed eCRF **(Exhibit GKK # 38, Page 1).** The audit history captured the date and time when the PI's re-signs eCRFs, **Exhibit GKK # 38, Page 1).**

  Dr. Tabuteau acknowledged the oversight and indicated that mitigating corrective action will be implemented going forward.

ADDITIONAL INFORMATION
A USB drive containing the original copies of the files for the collected exhibits is attached to the report as **Exhibit GKK # 33.**

(b) (7)(E), (b) (7)(C)

SAMPLES COLLECTED
No samples were collected during this inspection.
VOLUNTARY CORRECTIONS

No voluntary corrections were observed during this inspection.

EXHIBITS COLLECTED

GKK # 1: Opening meeting presentation	29
GKK # 2: Protocol # (b) (4) (b) (4) work agreements	09
GKK # 3: Protocol # (b) (4) (b) (4) work agreements	29
GKK # 4: Protocol # (b) (4) (b) (4) work agreements	07
GKK # 5: Protocol # (b) (4) (b) (4) . work agreements	07
GKK # 6: Protocol # (b) (4) (b) (4) work agreements	02
GKK # 7: Protocol # (b) (4) & (b) (4) . work agreements	38
GKK # 8: List of protocol # (b) (4) third party contractors	01
GKK # 9: Protocol # (b) (4) (b) (4) work agreements	09
GKK # 10: Protocol # (b) (4) (b) (4) work agreements	10
GKK # 11: Protocol # (b) (4) (b) (4) Database work agreements	08
GKK # 12: Protocol # (b) (4) (b) (4) work agreements	19
GKK # 13: Protocol # (b) (4) (b) (4) work agreements	06
GKK # 14: Protocol # (b) (4) (b) (4) work agreements	14
GKK # 15: Protocol # (b) (4) (b) (4) work agreements	18
GKK # 16: Protocol # (b) (4) Clincaltrial.gov extension approval	06
GKK # 17: Protocol # (b) (4) & (b) CRA job descriptions	02
GKK # 18: Protocol # (b) (4) Clinical trial monitoring plan	15
GKK # 19: Protocol # (b) (4) Clinical trial monitoring plan	51
GKK # 20: (b) (4) investigational brochure	77
GKK # 21: Protocol (b) (4) safety management plan	31
GKK # 22: Protocol (b) (4) safety management plan	32
GKK # 23: Protocol (b) (4) SAE reclassification	39
GKK # 24: List of clinical studies included in (b) (4) submission	05
GKK # 25: Protocol # (b) (4) clinical data management plan	11
GKK # 26: Protocol # (b) (4) clinical data management plan	17
GKK # 27: Protocol # (b) (4) clinicaltrial.gov information	10
GKK # 28: Example unsigned CRFs Protocol # (b) (4)	53
GKK # 29: Protocol # (b) (4) changes to CRFs	06
GKK # 30: (b) (6) CV and Monitoring activities	19
GKK # 31: (b) (6) CV and Monitoring activities	14
GKK # 32: (b) (4) database audit trail screen shots	03
GKK # 33: USB Drive Containing Original Copies of Exhibits	01

ATTACHMENTS

Attachment 1: Form FDA 482 issued on 6/21/2021 to Herriot (NMI) Tabuteau	03
Attachment 2: Assignment memo dated 5/4/2021	10

Geoffrey K. Kilili -S

Digitally signed by Geoffrey K. Kilili -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001340132, cn=Geoffrey K. Kilili -S
Date: 2021.07.15 11:36:15 -04'00'