

**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549

**FORM 8-K**

**CURRENT REPORT  
Pursuant to Section 13 or 15(D)  
of the Securities Exchange Act of 1934**

**December 16, 2019**  
Date of report (Date of earliest event reported)

**Axsome Therapeutics, Inc.**  
(Exact name of registrant as specified in its charter)

**Delaware**  
(State or other jurisdiction  
of incorporation)

**001-37635**  
(Commission  
File Number)

**45-4241907**  
(IRS Employer  
Identification No.)

**200 Broadway, 3rd Floor**  
**New York, New York**  
(Address of principal executive offices)

**10038**  
(Zip Code)

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

(Former name or former address, if changed since last report)

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

<u>Title of each class:</u>	<u>Trading Symbol(s)</u>	<u>Name of each exchange on which registered:</u>
Common Stock, Par Value \$0.0001 Per Share	AXSM	The Nasdaq Global Market

Check the appropriate box below if the Form 8-K is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425).
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12).
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b)).
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c)).

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company

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

**Item 8.01. Other Events.**

On December 16, 2019, Axsome Therapeutics, Inc. (the “Company”) issued a press release announcing that AXS-05 met the prespecified primary endpoint and significantly improved symptoms of depression in the Company’s GEMINI Phase 3 trial in major depressive disorder (“MDD”). The Company will host a conference call at 8:00 a.m. ET on December 16, 2019 to discuss the topline results of the GEMINI trial of AXS-05 in MDD.

The full text of the press release is filed as Exhibit 99.1 hereto and is incorporated herein by reference. A copy of the presentation that the Company will use in connection with the conference call is filed as Exhibit 99.2 hereto and is incorporated herein by reference.

**Item 9.01. Financial Statements and Exhibits.**

**(d) Exhibits.**

<u>Exhibit No.</u>	<u>Description</u>
99.1	<a href="#">Press Release dated December 16, 2019.</a>
99.2	<a href="#">GEMINI Presentation.</a>

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

**Axsome Therapeutics, Inc.**

Dated: December 16, 2019

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



**Axsome Therapeutics Announces AXS-05 Achieves Primary Endpoint in GEMINI Phase 3 Trial in Major Depressive Disorder**

*Demonstrated rapid, durable, and statistically significant improvement in depressive symptoms as measured by MADRS total score compared to placebo (p=0.002 on primary endpoint)*

*Statistically significant improvement at week 1 in MADRS total score compared to placebo (key secondary endpoint, p=0.007)*

*Statistically significant improvement versus placebo on all secondary endpoints at week 6, including remission (p<0.001), disease severity (p=0.002), functional impairment (p=0.002), and quality of life (p=0.011)*

*Positive results support NDA filing of AXS-05 for MDD, anticipated in 2H 2020*

*Potentially first-and-only, oral NMDA receptor antagonist with multimodal activity for the treatment of depression*

*Company to host conference call today at 8:00 AM ET*

NEW YORK, December 16, 2019 (Globe Newswire) – Axsome Therapeutics, Inc. (NASDAQ: AXSM), a clinical-stage biopharmaceutical company developing novel therapies for the management of central nervous system (CNS) disorders, today announced that AXS-05, a novel, oral, investigational NMDA receptor antagonist with multimodal activity, met the primary endpoint and rapidly and significantly improved symptoms of depression in the GEMINI Phase 3 trial in major depressive disorder (MDD). The GEMINI study was a randomized, double-blind, placebo-controlled, multi-center, U.S. trial, in which 327 adult patients with confirmed moderate to severe MDD were randomized to treatment with either AXS-05 (dextromethorphan/bupropion modulated delivery tablet) or placebo once daily for the first 3 days and twice daily thereafter for a total of 6 weeks.

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

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

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

"AXS-05 demonstrated a rapid and very clinically meaningful improvement in depressive symptoms, observed after only one week, in this large and well-controlled Phase 3 trial in major depressive disorder. Given the known challenges of conducting trials in psychiatry, it is very encouraging to see replication of Phase 2 findings in such a robust way," said Professor Maurizio Fava, MD, Psychiatrist-in-Chief at Massachusetts General Hospital (MGH), Director of the Division of Clinical Research of the MGH Research Institute, and Associate Dean for Clinical & Translational Research at Harvard Medical School. "Clinical depression is a potentially life-threatening condition. Currently marketed antidepressants fail to provide adequate treatment response in almost two thirds of treated patients, and may take up to six to eight weeks to provide clinically meaningful response. These data suggest that AXS-05, as an oral NMDA receptor antagonist with multimodal activity, may represent a novel treatment for major depressive disorder."

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

"We are very pleased with the compelling results of the GEMINI trial which demonstrate the potential for AXS-05 to provide significant benefits to patients living with depression, based on observed rapid and sustained antidepressant effects, resulting from its potentially first-in-class, oral NMDA receptor antagonist and multimodal mechanism of action," said Herriot Tabuteau, MD, Chief Executive Officer of Axsome. "The progress of the AXS-05 clinical program in mood disorders reflects Axsome's commitment to accelerating innovation to address serious CNS disorders. With GEMINI and the previously completed ASCEND study, the efficacy of AXS-05 in major depressive disorder has now been demonstrated in two positive well-controlled trials, enabling the filing of an NDA for AXS-05, which is anticipated in the coming year."

AXS-05 was granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of MDD in March 2019. Based on the outcome of the FDA Breakthrough Therapy meeting, Axsome believes the positive results of the GEMINI trial, along with the previously completed ASCEND trial of AXS-05 in MDD, are sufficient to support submission of a New Drug Application (NDA) for AXS-05 for the treatment of MDD. Axsome plans to file the NDA in the second half of 2020.

"Depression is a major public health concern with most patients failing to adequately respond to currently approved antidepressants," said Cedric O'Gorman, MD, Senior Vice President of Clinical Development and Medical Affairs of Axsome. "The potentially fatal consequences of depression highlight the need to rapidly and effectively control depressive symptoms. The positive results of the GEMINI study are significant and exciting because they bring us closer to our goal of addressing this public health need with a potentially first-in-class, rapid-acting, effective, oral, antidepressant which can be safely administered at home. With its modulation of glutamate neurotransmission, if approved, AXS-05 would represent the first mechanistically-novel oral pharmacotherapy for depression in over 30 years."

AXS-05 is a novel, oral, non-competitive NMDA receptor antagonist, also known as a glutamate receptor modulator, a new mechanism of action which is thought to help enhance synaptic connections and improve the communication between brain cells in people with major depressive disorder. In addition, AXS-05 is a sigma-1 receptor agonist; enhances brain levels of serotonin, noradrenaline, and dopamine, which are key neurotransmitters involved in the regulation of mood; and displays anti-inflammatory properties, which may be relevant to treating MDD. The multimodal actions of AXS-05 may be complementary and synergistic for the treatment of this biologically-based condition. AXS-05 is covered by 41 issued U.S. and international patents providing protection out to 2034, and Axsome maintains worldwide rights.

Detailed study results, including additional secondary endpoints, will be submitted for presentation at upcoming medical meetings and for publication. AXS-05 is also being evaluated in the STRIDE-1 Phase 3 trial in patients with treatment resistant depression (TRD), defined as patients with MDD who have failed two or more antidepressant treatments, and in the ADVANCE-1 trial in patients with Alzheimer's disease agitation. AXS-05 was granted Fast Track designations by the FDA for the treatment of TRD and for the treatment of Alzheimer's disease agitation.

## Summary of Topline Results of the GEMINI Trial

### *Effect on Depressive Symptoms*

- AXS-05 was associated with a statistically significant mean reduction from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score of 16.6 points for AXS-05 compared to 11.9 for placebo at Week 6 ( $p=0.002$ ).
- Remission, an absence of clinically significant symptoms of depression, prospectively defined as a MADRS total score of  $\leq 10$ , was seen at Week 6 in 39.5% of patients who received AXS-05, compared to 17.3% of patients who received placebo ( $p<0.001$ ).
- Response, defined as a  $\geq 50\%$  improvement in the MADRS total score, was seen at Week 6 in 54.0% of patients who received AXS-05, compared to 34.0% of patients who received placebo ( $p<0.001$ ).
- All secondary endpoints improved in favor of AXS-05 and achieved statistical significance at Week 6 (e.g. PGI-I, CGI-S, CGI-I, QIDS-SR-16, MADRS-6, etc.).

### *Time Course of Effect on Depressive Symptoms*

- AXS-05 demonstrated a statistically significant mean reduction from baseline in the MADRS total score of 7.3 points for AXS-05 compared to 4.9 points for placebo at Week 1 ( $p=0.007$ ), with statistical significance for this measure maintained at all time points thereafter.
- Statistically significant improvements at Week 1 were also observed for the PGI-I ( $p=0.008$ ), CGI-S ( $p=0.013$ ), CGI-I ( $p=0.035$ ), QIDS-SR-16 ( $p=0.016$ ), MADRS-6 ( $p=0.019$ ), and other endpoints. Statistically significant effects on these measures were generally maintained at all time points thereafter.
- Remission rates were statistically significantly greater for AXS-05 as compared to placebo at Week 2 ( $p=0.013$ ) and at every time point thereafter.

### *Quality of Life and Functional Impairment*

- AXS-05 was associated with a statistically significant improvement in quality of life, as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF), compared to placebo at Week 1 ( $p=0.031$ ), and at every time point thereafter ( $p=0.011$ , at Week 6).
- AXS-05 was associated with a statistically significant reduction in functional impairment, as measured by the Sheehan Disability Scale (SDS), compared to placebo at Week 2 ( $p=0.003$ ), and at every time point thereafter ( $p=0.002$ , at Week 6).

### *Safety and Tolerability*

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

## Conference Call Information

Axsome will host a conference call and webcast with slides today at 8:00 AM Eastern to discuss the topline results of the GEMINI trial of AXS-05 in major depressive disorder. To participate in the live conference call, please dial (844) 698-4029 (toll-free domestic) or (647) 253-8660 (international), and use the passcode 1022339. The live webcast can be accessed on the “Webcasts & Presentations” page of the “Investors” section of the Company’s website at axsome.com. A replay of the webcast will be available for approximately 30 days following the live event.

### About the GEMINI Trial

GEMINI (Glutamatergic and Monoaminergic Modulation in Depression) was a Phase 3, randomized, double-blind, multicenter, placebo-controlled trial of AXS-05 in patients with major depressive disorder (MDD) conducted in the U.S. A total of 327 patients with a confirmed diagnosis of moderate to severe MDD were randomized in a 1:1 ratio to receive AXS-05 (45 mg dextromethorphan/105 mg bupropion) (n=163), or placebo (n=164), twice daily for 6 weeks. The mean Montgomery-Åsberg Depression Rating Scale (MADRS) total scores at baseline were 33.6 for the AXS-05 group and 33.2 for the placebo group. The primary endpoint of the study was the change from baseline in the MADRS total score at Week 6. Secondary endpoints included MADRS change at Weeks 1 and 2, remission, response, Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), Patient Global Impression-Improvement (PGI-I), MADRS-6, Sheehan Disability Scale (SDS), other quality of life measures, safety and tolerability. P-values were calculated based on least square mean estimates.

### About Major Depressive Disorder (MDD)

Major depressive disorder (MDD) is a debilitating, chronic, biologically-based disorder characterized by low mood, inability to feel pleasure, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms, and which impairs social, occupational, educational, or other important functioning. In severe cases, MDD can result in suicide. According to the National Institutes of Health, an estimated 7.1% of U.S. adults, or approximately 17 million, experience MDD each year<sup>1</sup>. According to the World Health Organization (WHO), depression is the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease<sup>2</sup>. Nearly two thirds of diagnosed and treated patients do not experience adequate treatment response with currently available first-line therapy<sup>3</sup>, highlighting the need for additional therapies with new mechanisms of action. The majority of initial failures also fail second-line treatment. Patients diagnosed with MDD are defined as having treatment resistant depression (TRD) if they have failed to respond to two or more antidepressant therapies.

### About the Montgomery-Åsberg Depression Rating Scale (MADRS)

The Montgomery-Åsberg Depression Rating Scale (MADRS) is a well-established, 10-item, validated rating scale used to provide an assessment of depression, and as a guide to evaluate recovery. This scale is an accepted regulatory endpoint for depression. The scale is used in clinical research to rate the severity of a patient’s depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation, anxiety, weight loss, and somatic symptoms.

### About AXS-05

AXS-05 is a novel, oral, patent-protected, investigational NMDA receptor antagonist with multimodal activity under development for the treatment of major depressive disorder and other central nervous system (CNS) disorders. AXS-05 consists of a proprietary formulation and dose of dextromethorphan and bupropion and utilizes Axsome’s metabolic inhibition technology. The dextromethorphan component of AXS-05 is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, also known as a glutamate receptor modulator, which is a novel mechanism of action, meaning it works differently than currently approved therapies for major depressive disorder. The dextromethorphan component of AXS-05 is also a sigma-1 receptor agonist, nicotinic acetylcholine receptor antagonist, and inhibitor of the serotonin and norepinephrine transporters. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. AXS-05 is covered by more than 41 issued U.S. and international patents which provide protection out to 2034. AXS-05 has been granted U.S. Food and Drug Administration (FDA) Breakthrough Therapy designation for the treatment of MDD. AXS-05 is not approved by the FDA.

## About Axsome Therapeutics, Inc.

Axsome Therapeutics, Inc. is a clinical-stage biopharmaceutical company developing novel therapies for the management of central nervous system (CNS) disorders for which there are limited treatment options. Axsome's core CNS product candidate portfolio includes four clinical-stage candidates, AXS-05, AXS-07, AXS-09, and AXS-12. AXS-05 is currently in a Phase 3 trial in treatment resistant depression (TRD), a Phase 3 trial in major depressive disorder (MDD), and a Phase 2/3 trial in agitation associated with Alzheimer's disease (AD). AXS-05 is also being developed for smoking cessation treatment. AXS-07 is currently in two Phase 3 trials for the acute treatment of migraine. AXS-12 is being developed for the treatment of narcolepsy. AXS-05, AXS-07, AXS-09, and AXS-12 are investigational drug products not approved by the FDA. For more information, please visit the Company's website at [axsome.com](http://axsome.com). The Company may occasionally disseminate material, nonpublic information on the company website.

## References

1. National Institute of Mental Health. (2017). Major Depression. Retrieved from <https://www.nimh.nih.gov/health/statistics/major-depression.shtml>.
2. World Health Organization. Fact Sheets: Depression, accessed October 9, 2018, <http://www.who.int/en/news-room/fact-sheets/detail/depression>.
3. Rush AJ, et al. (2007) *Am J. Psychiatry* 163:11, pp. 1905-1917 (STAR\*D Study).

## Forward Looking Statements

Certain matters discussed in this press release are "forward-looking statements". We may, in some cases, use terms such as "predicts," "believes," "potential," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company's statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including our ability to fully fund our disclosed clinical trials, which assumes no material changes to our currently projected expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of our ongoing clinical trials, and the number or type of studies or nature of results necessary to support the filing of a new drug application ("NDA") for any of our current product candidates; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration ("FDA") or other regulatory authority approval of, or other action with respect to, our product candidates (including, but not limited to, FDA's agreement with the Company's plan to discontinue the bupropion treatment arm of the ADVANCE-1 study in accordance with the independent data monitoring committee's recommendations); the potential for the ASCEND clinical trial, combined with the GEMINI clinical trial results, to provide a basis for approval of AXS-05 for the treatment of major depressive disorder and accelerate its development timeline and commercial path to patients; the Company's ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company's research and development programs and collaborations; the success of the Company's license agreements; the acceptance by the market of the Company's product candidates, if approved; the Company's anticipated capital requirements, including the Company's anticipated cash runway and the Company's current expectations regarding its plans for future equity financings prior to the readout from its Phase 3 trials; and other factors, including general economic conditions and regulatory developments, not within the Company's control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this press release and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance. The data disclosed in this press release are considered topline data and subject to further statistical review and the final results may vary.



**Axsome Contact:**

Mark Jacobson  
Senior Vice President, Operations  
Axsome Therapeutics, Inc.  
200 Broadway, 3rd Floor  
New York, NY 10038  
Tel: 212-332-3243  
Email: [mjacobson@axsome.com](mailto:mjacobson@axsome.com)  
[www.axsome.com](http://www.axsome.com)

 NASDAQ: AXSM

# AXSOME

## THERAPEUTICS

GEMINI Phase 3 Trial of AXS-05 in MDD

Topline Results

Conference Call

December 16, 2019

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# AXS-05 in Major Depressive Disorder (MDD)

## GEMINI Phase 3 Trial Topline Results

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<b>Introduction</b>	<b>Mark Jacobson</b> , Senior Vice President, Operations
<b>Overview and Summary</b>	<b>Herriot Tabuteau, MD</b> , Chief Executive Officer
<b>GEMINI Trial Design &amp; Results</b>	<b>Cedric O’Gorman, MD</b> , Senior Vice President, Clinical Development & Medical Affairs
<b>Q&amp;A</b>	<b>Presenters, Nick Pizzie</b> , Chief Financial Officer and <b>Dave Marek</b> , Chief Commercial Officer
<b>Concluding Remarks</b>	<b>Herriot Tabuteau, MD</b> , Chief Executive Officer

# Forward-Looking Statements & Safe Harbor

Certain information contained in this presentation may include "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as "predicts," "believes," "potential," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company's statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including our ability to fully fund our disclosed clinical trials, which assumes no material changes to our currently projected expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of our ongoing clinical trials and the number or type of studies or nature of results necessary to support the filing of a new drug application for any of our current product candidates; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration ("FDA") or other regulatory authority approval of, or other action with respect to, our product candidates (including, but not limited to, FDA's agreement with the Company's plan to discontinue the bupropion treatment arm of the ADVANCE-1 study in accordance with the independent data monitoring committee's recommendations); the Company's ability to obtain additional capital necessary to fund its operations; the Company's ability to generate revenues in the future; the potential for the ASCEND clinical trial, combined with the GEMINI clinical trial results, to provide a basis for approval of AXS-05 for the treatment of major depressive disorder and accelerate its development timeline and commercial path to patients; the Company's ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company's research and development programs and collaborations; the enforceability of the Company's license agreements; the acceptance by the market of the Company's product candidates, if approved; the Company's anticipated capital requirements, including the Company's anticipated cash runway and the Company's current expectations regarding its plans for future equity financings prior to the readout from its Phase 3 clinical trials; and other factors, including general economic conditions and regulatory developments, not within the Company's control. These factors could cause actual results and developments to be materially different from those expressed in or implied by such statements. Forward-looking statements are not guarantees of future performance, and actual results may differ materially from those projected. The forward-looking statements are made only as of the date of this presentation and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such data after the date of this presentation. In addition, these projections, assumptions and estimates are necessarily subject to a high degree of uncertainty and risk. The data disclosed in this press release are considered topline data and subject to further statistical review and the final results may vary.



# Overview and Summary

**Herriot Tabuteau, MD**

AXSOME THERAPEUTICS

Chief Executive Officer  
Axsome Therapeutics, Inc.

# Summary of Topline Results:

## Rapid and Durable Effects with AXS-05

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- AXS-05: a novel, oral, investigational NMDA receptor antagonist with multimodal activity
- Rapid, durable, substantial, and significant improvement in symptoms of depression
- Met primary endpoint—highly statistically significant improvement on MADRS versus placebo at Week 6
- Rapid reduction in depressive symptoms at Week 1, earliest timepoint assessed
- Consistent effects—statistically significant improvement on multiple secondary endpoints versus placebo at Week 1 and thereafter
- AXS-05 was safe, well tolerated, and not associated with psychotomimetic effects
- Positive GEMINI trial, together with previously completed positive ASCEND trial, sufficient to support NDA filing of AXS-05 in MDD
  - Granted Breakthrough Therapy Designation for MDD earlier this year
  - NDA filing anticipated in 2H 2020

# Major Depressive Disorder (MDD): Need for New, Innovative Treatments

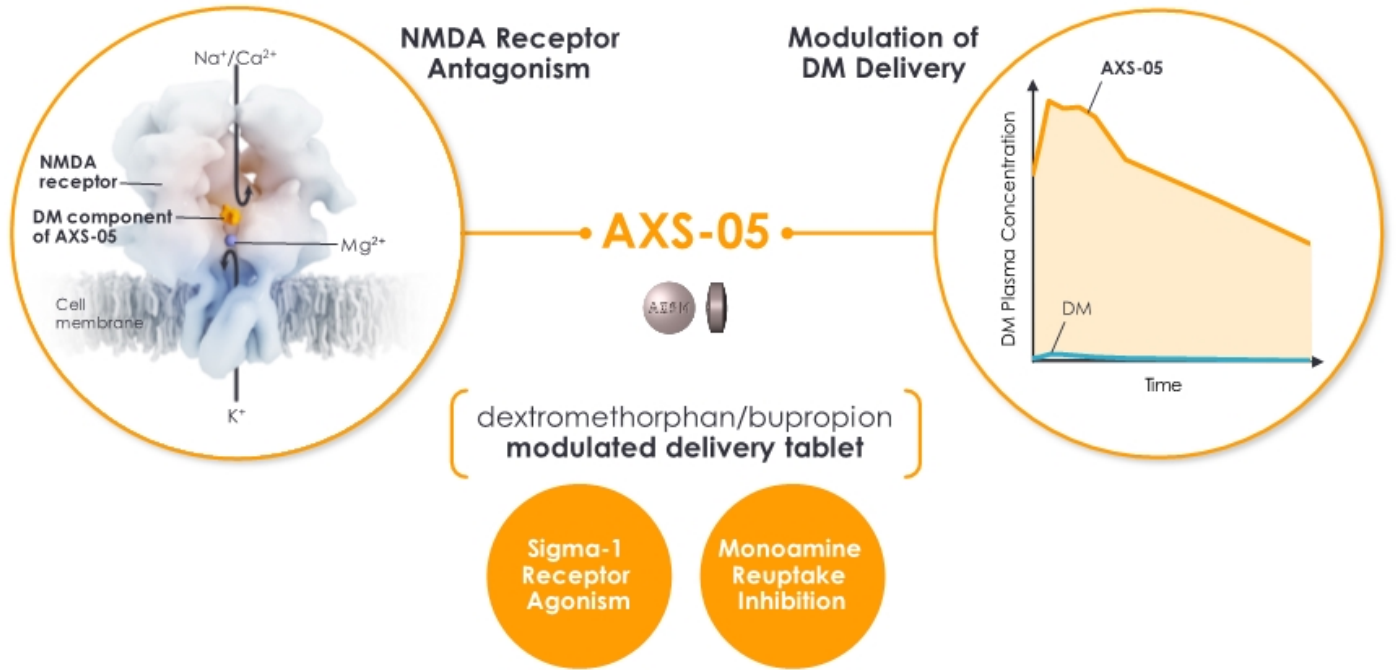
- Major depressive disorder (MDD) is a disabling and potentially life-threatening, biologically-based disorder
- Majority of patients experience inadequate response to current treatments: 63% fail to achieve remission to initial therapy, and of those 69% fail second line therapy<sup>2</sup>
- Current antidepressants are associated with prolonged time to clinical response: up to 6-8 weeks for those who respond
- All currently approved oral MDD agents work primarily through monoaminergic mechanisms
- Urgent need exists for new treatments with novel mechanisms of action, and faster onset of action, that are orally administered

**17** million

U.S. adults experience major depressive episodes each year<sup>1</sup>

1. National Survey on Drug Use and Health (NSDUH). (2017).  
2. Rush AJ, et al. *Am J Psychiatry* 2006;163:1905-1917.

# AXS-05: Novel, Oral, NMDA Receptor Antagonist with Multimodal Activity



Abbreviations: DM = Dextromethorphan; Mg<sup>2+</sup>=magnesium ion; Na+=sodium ion; Ca<sup>2+</sup>=calcium ion; K+=potassium ion. Axsome data on file





# GEMINI Phase 3 Trial Design & Results

**Cedric O’Gorman MD, MBA**

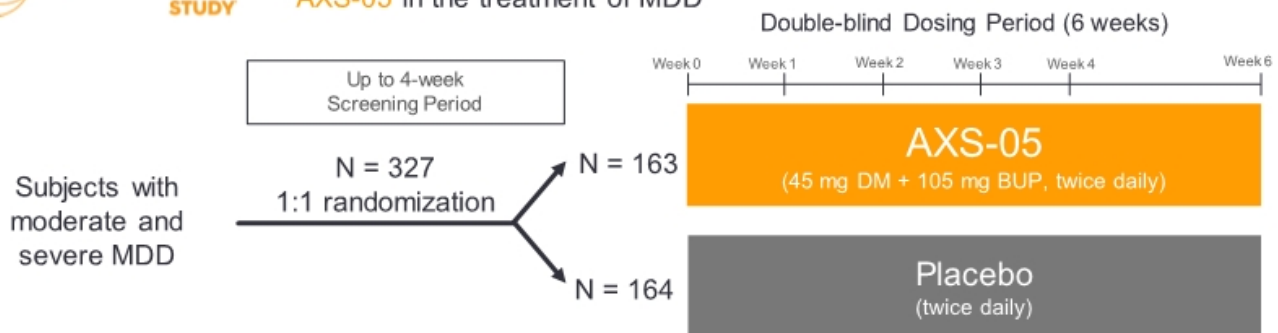
AXSOME THERAPEUTICS

Senior Vice President, Clinical Development and Medical Affairs  
Axsome Therapeutics, Inc.

# GEMINI Phase 3 Trial: Design Summary



A Phase 3 trial to assess the efficacy and safety of  
AXS-05 in the treatment of MDD



BUP = Bupropion; DM = Dextromethorphan

- **Primary Endpoint:**

- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6

- **Key Secondary Endpoints:**

- MADRS change at Week 1 and Week 2; MADRS remission ( $\leq 10$ ) at Week 6; MADRS response ( $\geq 50\%$ ) at Week 6

- **Secondary Endpoints:**

- Clinical Global Impression of Improvement (CGI-I), Clinical Global Impression of Severity (CGI-S), Patient Global Impression of Improvement (PGI-I), Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16), Sheehan Disability Scale (or SDS), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF)

AXSOME THERAPEUTICS

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# GEMINI Phase 3 Trial:

## Key Entry Criteria

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**Inclusion criteria included:**

- Male or female 18-65 years of age inclusive
- DSM-5 criteria for current MDD without psychotic features
- Montgomery-Åsberg Depression Rating Scale (MADRS) total score of  $\geq 25$
- CGI-S score of  $\geq 4$  at baseline

**Exclusion criteria included:**

- History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation or any experimental central nervous system treatment during the current episode or in the past 6 months
- Schizophrenia, bipolar disorder, obsessive compulsive disorder
- Psychiatric symptoms secondary to any other general medical condition

# GEMINI Phase 3 Trial:

## Demographics and Baseline Characteristics

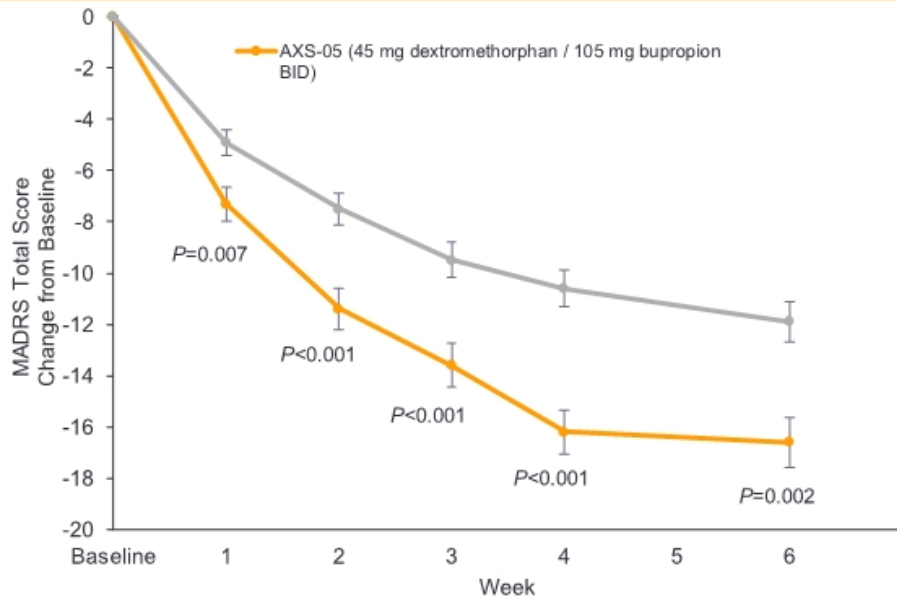
	<b>AXS-05 (45 mg DM / 105 mg BUP)</b>	<b>Placebo</b>
<b>Age (years)</b>	42.1 (12.71)	41.1 (13.78)
<b>Female Gender, n (%)</b>	98 (60.1%)	117 (71.3%)
<b>Race, n (%)</b>		
<b>White</b>	88 (54.0%)	92 (56.1%)
<b>Black or African American</b>	61 (37.4%)	55 (33.5%)
<b>Asian</b>	9 (5.5%)	8 (4.9%)
<b>Other or Not Reported</b>	5 (3.1%)	9 (5.5%)
<b>BMI (mg/kg<sup>2</sup>)</b>	29.2 (5.59)	29.4 (5.66)
<b>MADRS Total Score</b>	33.6 (4.43)	33.2 (4.36)
<b>CGI-S Score</b>	4.6 (0.59)	4.6 (0.57)

Data are mean (SD) unless otherwise stated.

Abbreviations: BMI = Body Mass Index; BUP = bupropion; CGI-S = Clinical Global Impression – Severity; DM = dextromethorphan; MADRS = Montgomery-Åsberg Depression Rating Scale

- Demographics and baseline characteristics were similar across both treatment groups
- Study completion rates were greater than 75% in both treatment groups

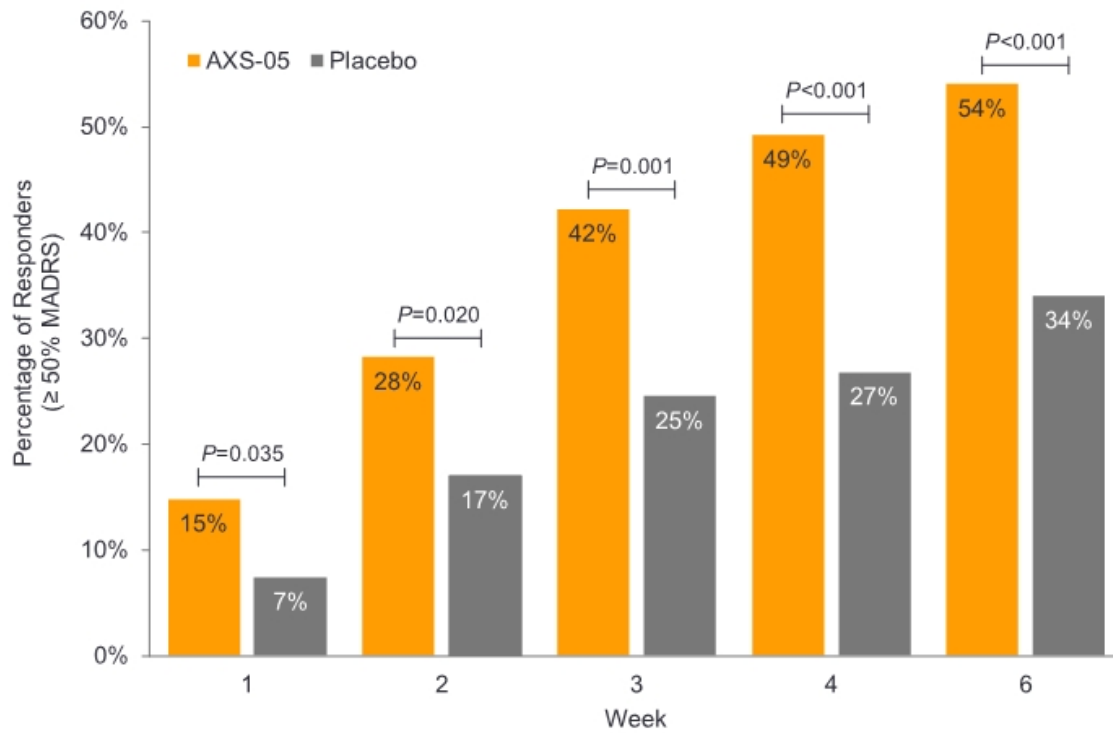
# Improvement in Depressive Symptoms: Primary Endpoint – Change in MADRS Total Score



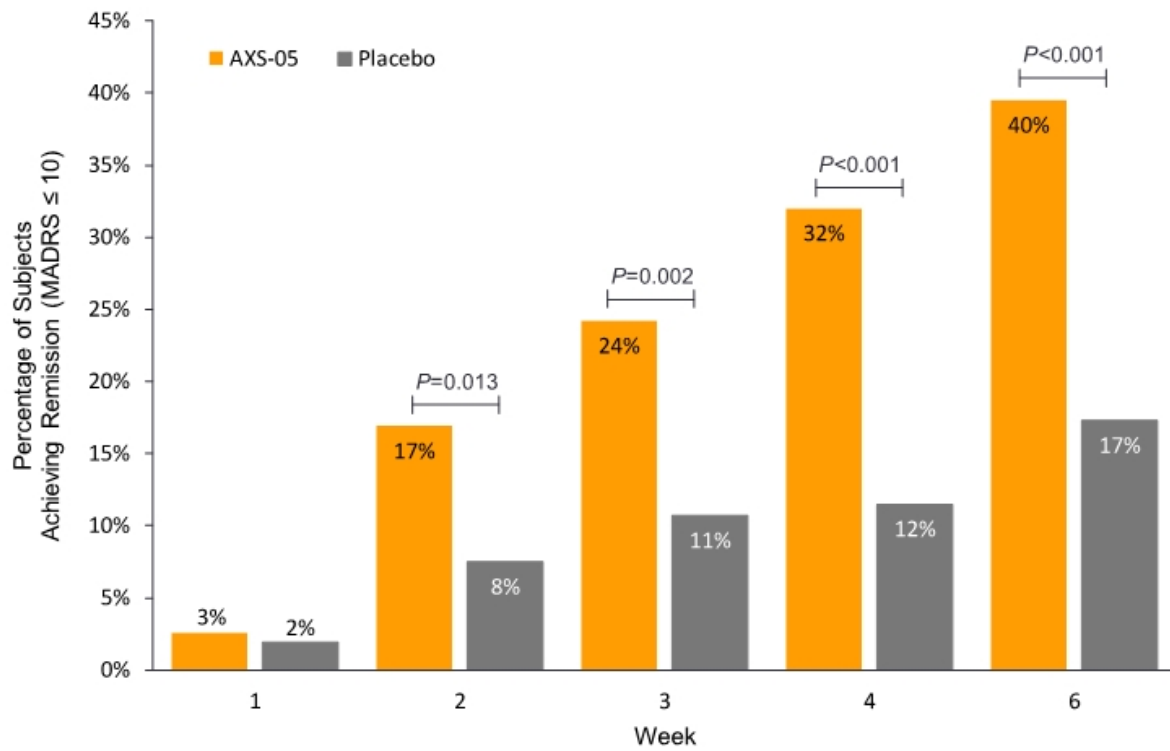
	AXS-05 (n=156)	Placebo (n=162)	Difference	P-Value
<b>Primary Endpoint</b>				
Change in MADRS Total Score at Week 6	-16.6	-11.9	-4.7	0.002
<b>Key Secondary Endpoint</b>				
Change in MADRS Total Score at Week 1	-7.3	-4.9	-2.4	0.007

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

# Improvement in Depressive Symptoms: Clinical Response ( $\geq 50\%$ MADRS improvement)



# Improvement in Depressive Symptoms: Achievement of Remission (MADRS $\leq 10$ )



# Rapid and Durable Improvements: Treatment Effects with AXS-05

	P-value		
	Week 1	Week 2	Week 6
<b>Depressive Symptom Improvement</b>			
MADRS Total Score Change from Baseline	0.007	<0.001	0.002
Clinical Response ≥50% Reduction in MADRS from Baseline	0.035	0.020	<0.001
Remission MADRS Score of ≤10	ns	0.013	<0.001
Core Symptoms Change from Baseline in MADRS-6	0.019	0.014	0.011
QIDS-SR-16 Change from Baseline	0.016	<0.001	0.001
CGI-I % with Marked / Moderate Improvement	0.035	<0.001	0.016
CGI-S Change from Baseline	0.013	<0.001	0.002
PGI-I % Reporting Very Much / Much Improved	0.008	0.015	0.007
<b>Quality of Life and Functional Improvement</b>			
Q-LES-Q-SF Change from Baseline in % of Maximum Possible Score	0.031	0.017	0.011
SDS Total Score Change from Baseline	ns	0.003	0.002

Abbreviations: CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; MADRS = Montgomery-Åsberg Depression Rating Scale; ns = p-value not significant; PGI-I = Patient Global Impressions-Improvement; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Rated; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SDS = Sheehan disability scale.



# Safety of AXS-05 in MDD:

## Adverse Events Occurring in $\geq 5\%$ of Subjects

	<b>AXS-05</b> (N = 162)	<b>Placebo</b> (N = 164)
<b>Any Treatment-Emergent AE</b>	<b>100 (61.7%)</b>	<b>74 (45.1%)</b>
Dizziness	26 (16.0%)	10 (6.1%)
Nausea	21 (13.0%)	14 (8.5%)
Headache	13 (8.0%)	6 (3.7%)
Diarrhea	11 (6.8%)	5 (3.0%)
Somnolence	11 (6.8%)	5 (3.0%)
Dry mouth	9 (5.6%)	4 (2.4%)

Data presented as number of subjects (% of subjects)

- Rates of discontinuation due to adverse events were low in both groups, 6.2% and 0.6%, for AXS-05 and placebo, respectively
- One serious adverse event in the AXS-05 arm, which was not related to study drug

# GEMINI Phase 3 Trial Results:

## Summary

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- AXS-05 resulted in rapid, durable, substantial, and statistically significant improvements in depressive symptomatology across multiple efficacy endpoints
- Symptomatic benefits translated into statistically significant improvements on validated measurements of daily functioning and quality of life
- AXS-05 was safe and well tolerated in this trial



# Q&A

# Concluding Remarks

## Herriot Tabuteau, MD

Chief Executive Officer  
Axsome Therapeutics, Inc.

# AXS-05:

## Clinical Programs in Psychiatry

	Clinical Program				
	ASCEND	GEMINI	STRIDE-1	AXS-05 / OL	ADVANCE-1
<b>Indication</b>	MDD	MDD	TRD	MDD/TRD	Alzheimer's Agitation
<b>Phase</b>	Pivotal Phase 2	Pivotal Phase 3	Pivotal Phase 3	Open-label Phase 3	Pivotal Phase 2/3
<b>Objectives</b>	Efficacy of AXS-05 vs. BUP	Efficacy of AXS-05 vs. PBO	Efficacy of AXS-05 vs. BUP	Long-term safety of AXS-05	Efficacy of AXS-05 vs. BUP and PBO
<b>Status</b>	Completed	Completed	Enrollment complete	Ongoing	Ongoing

Abbreviations: BUP = bupropion; MDD = Major Depressive Disorder; OL = Open-label; PBO = placebo; TRD = Treatment Resistant Depression

- FDA Breakthrough Therapy designation granted for AXS-05 in MDD
- Positive results from GEMINI and ASCEND trials sufficient to support NDA filing of AXS-05 in the treatment of MDD, targeted for 2H 2020

# Our CNS Candidates and Pipeline

- Four differentiated clinical-stage CNS assets targeting significant and growing markets
- Patent protection to 2034-2036, worldwide rights

Product Candidate	Preclinical	Phase 1	Phase 2	Phase 3
AXS-05 (DM + BUP)	Treatment Resistant Depression: Fast Track Designation			Ongoing
	Major Depressive Disorder: Breakthrough Therapy Designation			
	Agitation in Alzheimer's Disease: Fast Track Designation			Ongoing
	Smoking Cessation			
AXS-07 (MoSEIC™ Mx + Riz)	Migraine: Special Protocol Assessment			Ongoing
AXS-12 (Reboxetine)	Narcolepsy; U.S. Orphan Designation			Phase 3 planned
AXS-09 (DM + S-BUP)	CNS Disorders			

Abbreviations: BUP = Bupropion; CNS = Central Nervous System; DM = Dextromethorphan; Mx = Meloxicam; Riz = Rizatriptan; S-BUP = Esbupropion.

# AXSOME

## THERAPEUTICS

Thank you.

For more information, please contact

Mark Jacobson  
SVP, Operations

212-332-3243  
mjacobson@Axsome.com

[axsome.com](http://axsome.com)

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