

AXSOME

THERAPEUTICS

ASCEND Phase 2 Trial of AXS-05 in MDD

Topline Results

Conference Call

January 7, 2019

AXS-05 in MDD

ASCEND Phase 2 Trial Topline Results

Introduction	Mark Jacobson , Senior Vice President, Operations
Overview and Summary	Herriot Tabuteau, MD , Chief Executive Officer
ASCEND Trial Design & Results	Cedric O’Gorman, MD , Senior Vice President, Clinical Development & Medical Affairs
Q&A	Presenters & Nick Pizzie , Chief Financial Officer
Concluding Remarks	Herriot Tabuteau, MD , Chief Executive Officer

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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 and completion of the trials, interim analyses and receipt of interim results; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration or other regulatory authority approval of, or other action with respect to, our product candidates; the potential for the ASCEND clinical trial 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 obtain additional capital necessary to fund its operations; the Company’s ability to generate revenues in the future; 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; the enforceability of the Company’s license agreements; the acceptance by the market of the Company’s product candidates, if approved; 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.

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Overview and Summary

Herriot Tabuteau, MD

Chief Executive Officer
Axsome Therapeutics, Inc.

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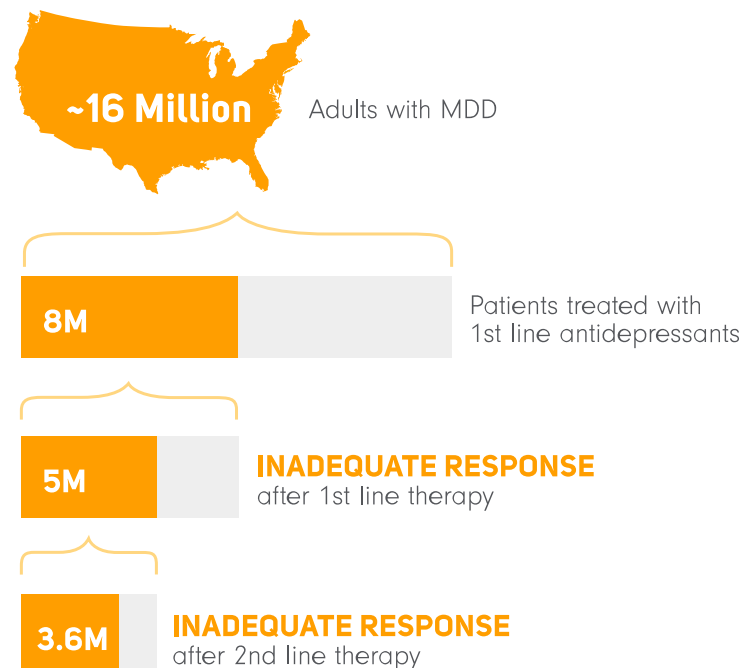
AXS-05: ASCEND Phase 2 Trial in MDD

Summary of Topline Results

- AXS-05: a novel, oral, investigational NMDA receptor antagonist with multimodal activity.
- Significantly and rapidly improved symptoms of depression.
- Met primary endpoint—highly statistically significant improvement on MADRS versus active comparator bupropion.
- Rapid reduction in depressive symptoms as early as Week 1, sustained through Week 6.
- Improvements with AXS-05 were substantial and statistically significant versus a well-established antidepressant.
- Consistent effects—greater improvement on multiple secondary endpoints for AXS-05 versus active comparator.
- AXS-05 was safe, well tolerated, and not associated with psychotomimetic effects, weight gain, or sexual dysfunction.
- Data support ongoing development of AXS-05 in treatment resistant depression and further development in MDD.

Major Depressive Disorder (MDD): Overview

- Leading cause of disability, and a major contributor to overall disease burden worldwide.
- As much as 70 % of patients have inadequate response to current first-line therapies.
 - Can take up to 6-8 weeks for clinically meaningful response.
- All approved MDD pharmacotherapies act primarily through monoaminergic mechanisms.
- Urgent need for new treatments with novel mechanisms of action, that are orally administered, and well-tolerated.

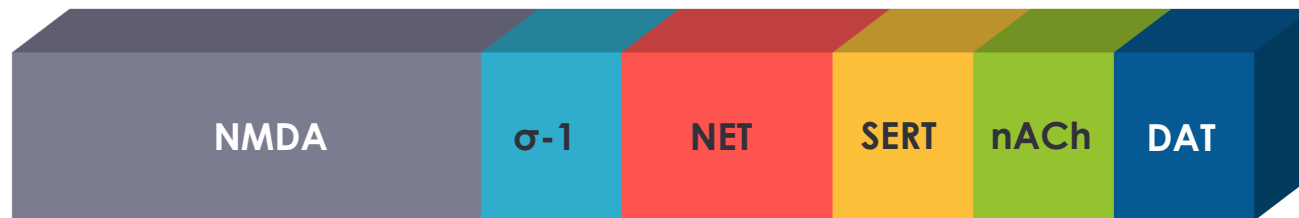


AXS-05: Novel Multimodal Therapy for CNS Disorders

Single Target



Multimodal



AXS-05
(Dextromethorphan/
Bupropion)

Abbreviations: σ -1 = Sigma-1; DAT = Dopamine Reuptake Transporter; nACh = Nicotinic Acetylcholine Receptor; NMDA = N-methyl-D-aspartate; NET = Norepinephrine Reuptake Transporter; SERT = Serotonin Reuptake Transporter.



ASCEND Trial Design & Results

Cedric O’Gorman, MD, MBA

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

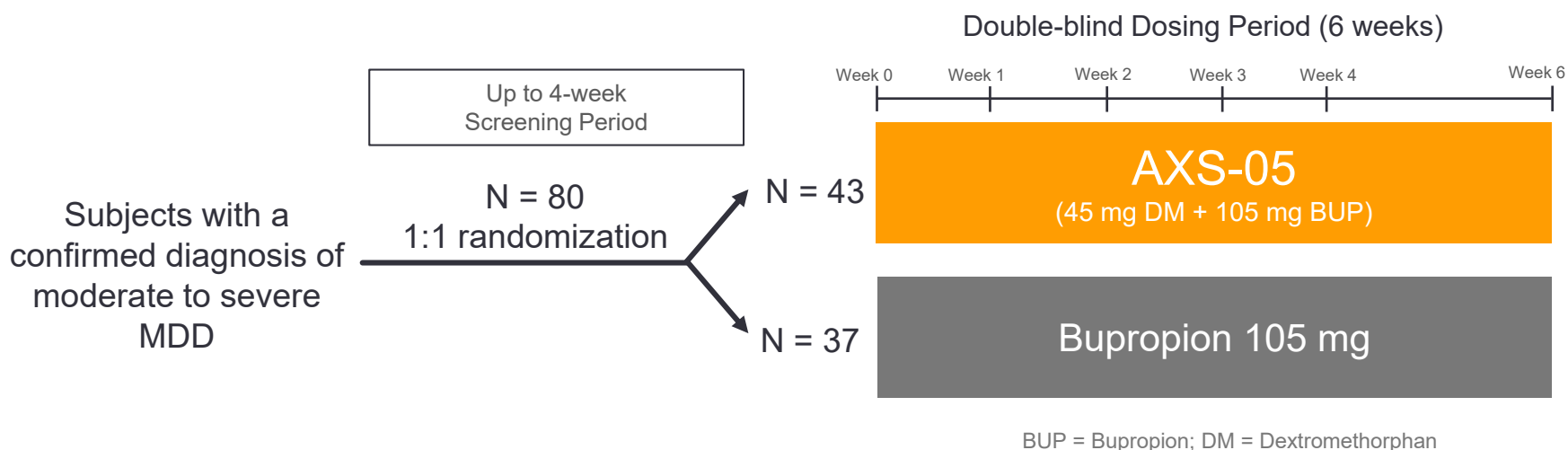
ASCEND:

Clinical Trial Design

- Phase 2, randomized, double-blind, active-controlled, multi-center, U.S. trial
- N=80 adult patients with confirmed diagnosis of moderate to severe MDD
- 6-week treatment period
 - Twice daily dosing
- Dose groups (1:1 randomization):
 - AXS-05 (45 mg dextromethorphan/105 mg bupropion)
 - Active comparator bupropion (105 mg)
- Extensive quality control measures

ASCEND: Clinical Trial Design

Assessing Clinical Episodes in Depression



Primary Endpoint:

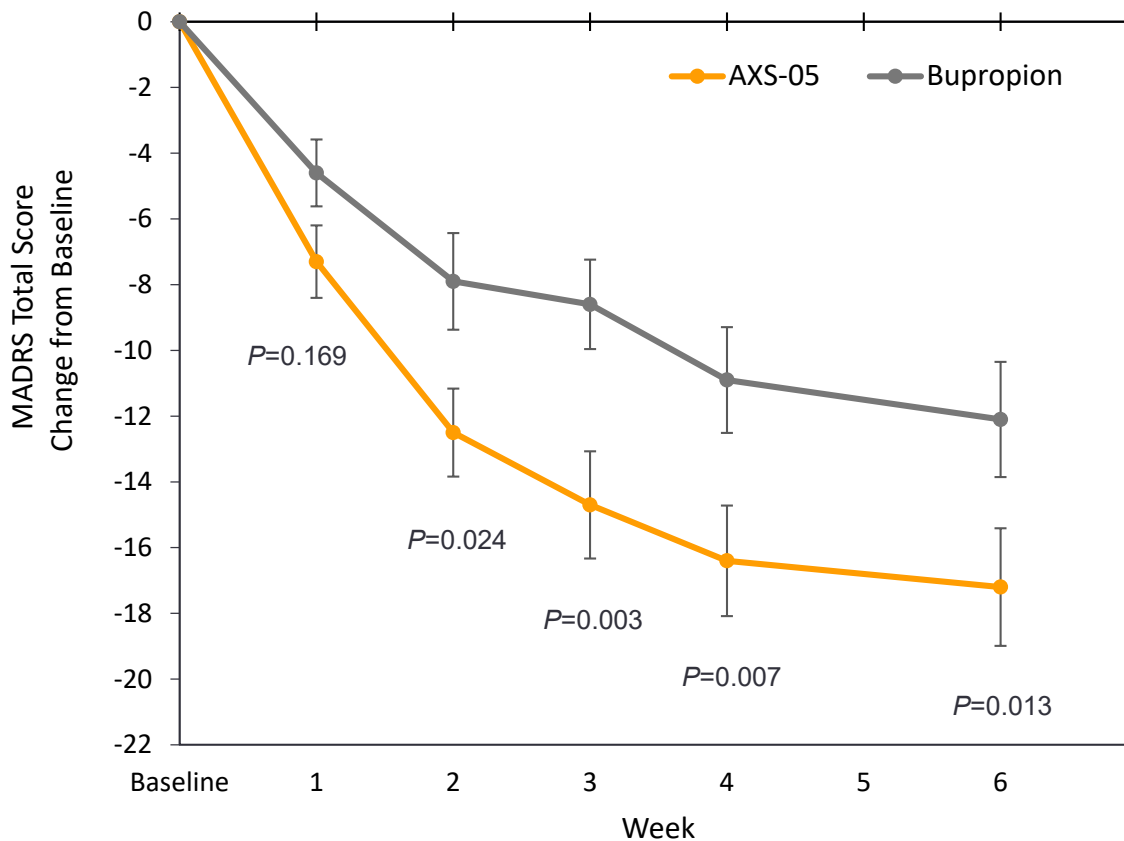
Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score over the 6-week treatment period (calculated at each time point and averaged)

ASCEND:

Demographics and Baseline Characteristics

- Mean age (years): 37.3 for AXS-05 group, 37.7 for bupropion group
- Mean age at onset of illness (years): 26.5 for AXS-05 group, 26.6 for bupropion group
- Mean MADRS total score at baseline: 31.8 for AXS-05 group, 32.2 for bupropion group
- 51% of subjects had 3 or more major depressive episodes prior to enrollment
- 23% of subjects had received prior first line treatment in their current major depressive episode

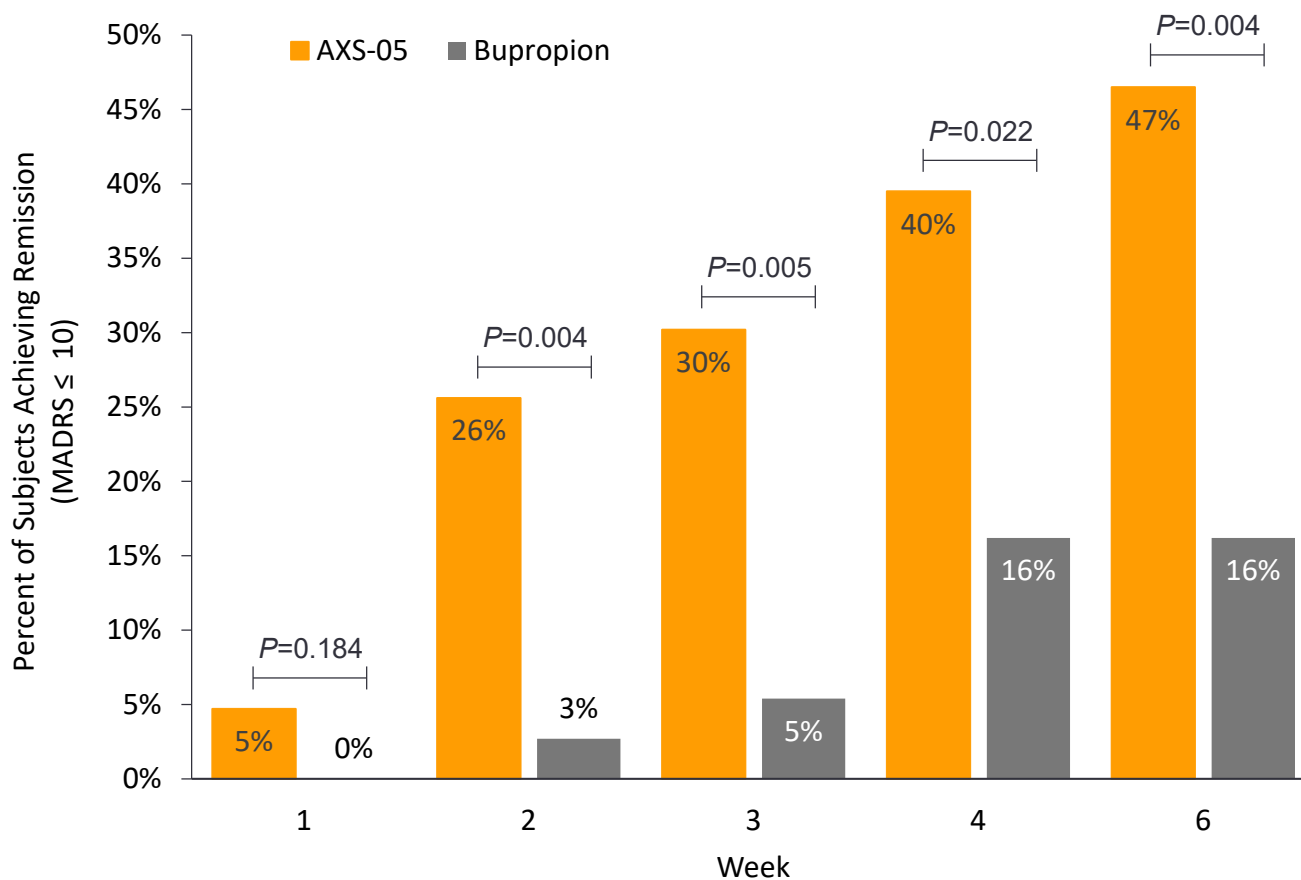
ASCEND: Primary Endpoint: Change in MADRS Total Score



	AXS-05	Bupropion	P-Value
Primary Endpoint			
Change in MADRS Total Score over 6-Week Period (averaged)	-13.7	-8.8	< 0.001
Change in MADRS Total Score at Week 6	-17.2	-12.1	0.013

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Secondary Endpoint: Achievement of Remission



ASCEND:

Secondary Endpoints

Secondary Endpoint	P-Value*
MADRS Total Score Change Weeks 1-2	0.01
% Achieving Remission on MADRS at Week 2	0.004
% Achieving Remission on MADRS at Week 6	0.004
MADRS-6 Change at Week 6	0.007
% of Responders on MADRS-6 ($\geq 50\%$ reduction from baseline) at Week 6	0.014
Clinical Global Impression-Improvement (CGI-I) at Week 1	0.045
CGI-I at Week 6	0.051
Clinical Global Impression-Severity (CGI-S) at Week 6	0.028

* P-values are for AXS-05 versus active comparator bupropion. Multiple secondary endpoints favored AXS-05.

ASCEND: Safety

- AXS-05 was safe and well tolerated with similar rates of adverse events in the AXS-05 and bupropion arms.
- No serious adverse events, and no meaningful difference between the two treatment arms in discontinuations due to adverse events.
- The most commonly reported adverse events in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite, and anxiety.
- AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.

ASCEND: Summary

- Statistically significant improvements on MADRS and secondary efficacy endpoints for AXS-05 in patients with MDD
- Early and sustained separation from active comparator bupropion
- Safe and well-tolerated with no psychotomimetic effects, weight gain, or increased sexual dysfunction



Q&A



Concluding Remarks

Herriot Tabuteau, MD

Chief Executive Officer
Axsome Therapeutics, Inc.

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AXS-05:

Conclusions and Ongoing Programs with AXS-05

- AXS-05 demonstrated significant and rapid antidepressant activity with a favorable safety profile in the ASCEND trial in MDD.
- Data support the continued development of this novel multimodal agent in MDD and other neuropsychiatric indications.
- **Major Depressive Disorder** – ASCEND Phase 2 trial completed
 - Positive topline results announced today
 - Detailed results to be presented at upcoming scientific meetings
- **Treatment Resistant Depression** – Phase 3 STRIDE-1 trial ongoing
 - Positive interim futility analysis announced
 - Topline results anticipated 1Q 2019
- **Alzheimer's Disease Agitation** – Phase 2/3 ADVANCE-1 trial ongoing
 - Positive interim futility analysis recently announced
 - Interim efficacy analysis anticipated 2019
- **Smoking Cessation** – Phase 2 trial under collaboration with Duke University
 - Topline results anticipated 1Q 2019

Clinical Milestones

Product Candidate	Indication	2019
AXS-05 (DM + BUP)	TRD	<ul style="list-style-type: none"> ● STRIDE-1 top-line results (1Q 2019)
	AD Agitation	<ul style="list-style-type: none"> ● ADVANCE-1 interim efficacy analysis ● ADVANCE-1 top-line results (2H 2019/1H 2020)
	MDD	<ul style="list-style-type: none"> ✓ ASCEND top-line results
	Smoking Cessation	<ul style="list-style-type: none"> ● Ph 2 top-line results (1Q 2019)
AXS-07 (MoSEIC™ Mx + Riz)	Migraine	<ul style="list-style-type: none"> ● Ph 3 trial start (1Q 2019) ● Ph 3 top-line results
AXS-12 (Reboxetine)	Narcolepsy	<ul style="list-style-type: none"> ● Ph 2 trial start (1Q 2019) ● Ph 2 top-line results (1H 2019)

Abbreviations: AD = Alzheimer's Disease; BUP = Bupropion; DM = Dextromethorphan; MDD = Major Depressive Disorder; Mx = Meloxicam; Riz = Rizatriptan; TRD = Treatment Resistant Depression.

✓ Accomplished milestone.

● Upcoming milestone.

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 Granted			Ongoing
	Agitation in Alzheimer's Disease: Fast Track Granted			Ongoing
	Major Depressive Disorder			
	Smoking Cessation			Ongoing
AXS-07 (MoSEIC™ Mx + Riz)	Migraine			
AXS-12 (Reboxetine)	Narcolepsy; U.S. Orphan Designation			
AXS-09 (DM + S-BUP)	CNS Disorders			

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

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Thank you.

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