NASDAQ: AXSM

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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Overview and Summary

Herriot Tabuteau, MD

AXSOME THERAPEUTICS

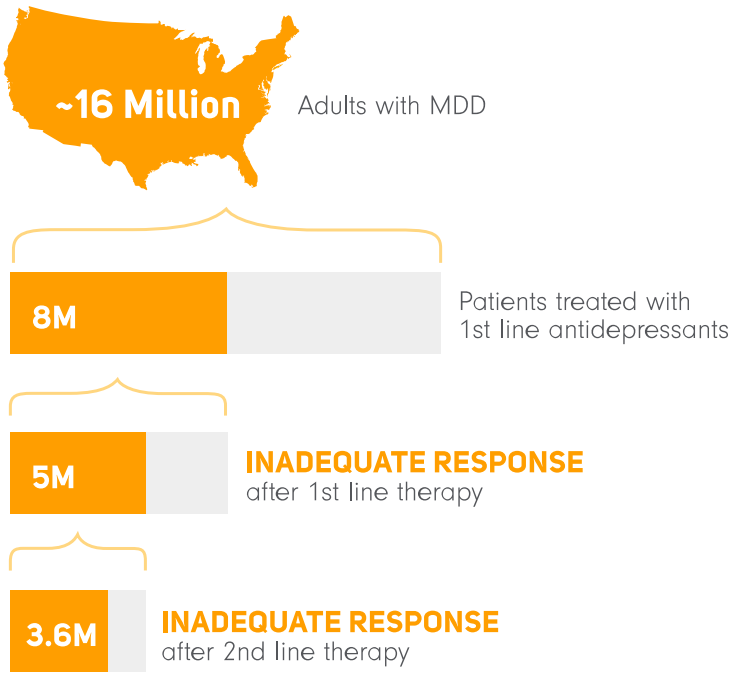
Chief Executive Officer
Axsome Therapeutics, Inc.

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.

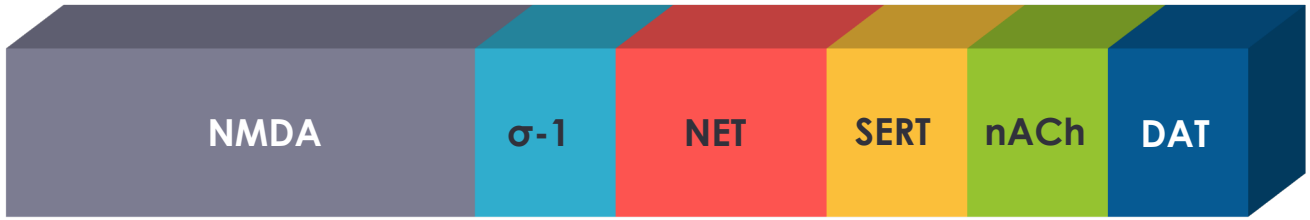


AXS-05:
Novel Multimodal Therapy for CNS Disorders

Single Target

Multimodal

Ketamine



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

AXSOME THERAPEUTICS

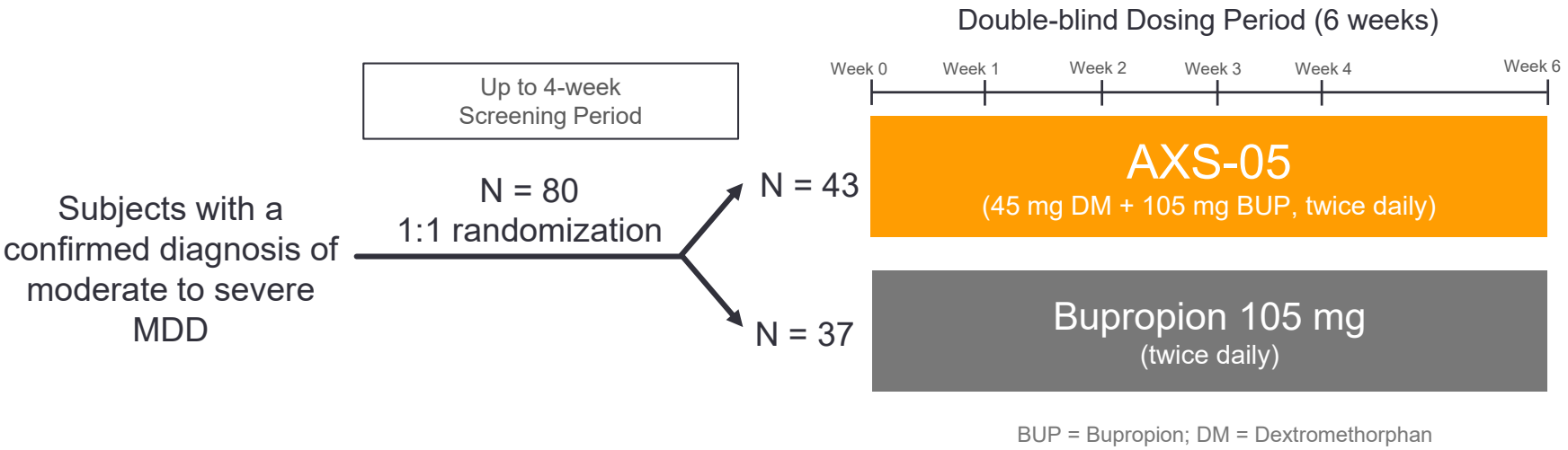
Senior Vice President, Clinical Development and Medical Affairs
Axsome Therapeutics, Inc.

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



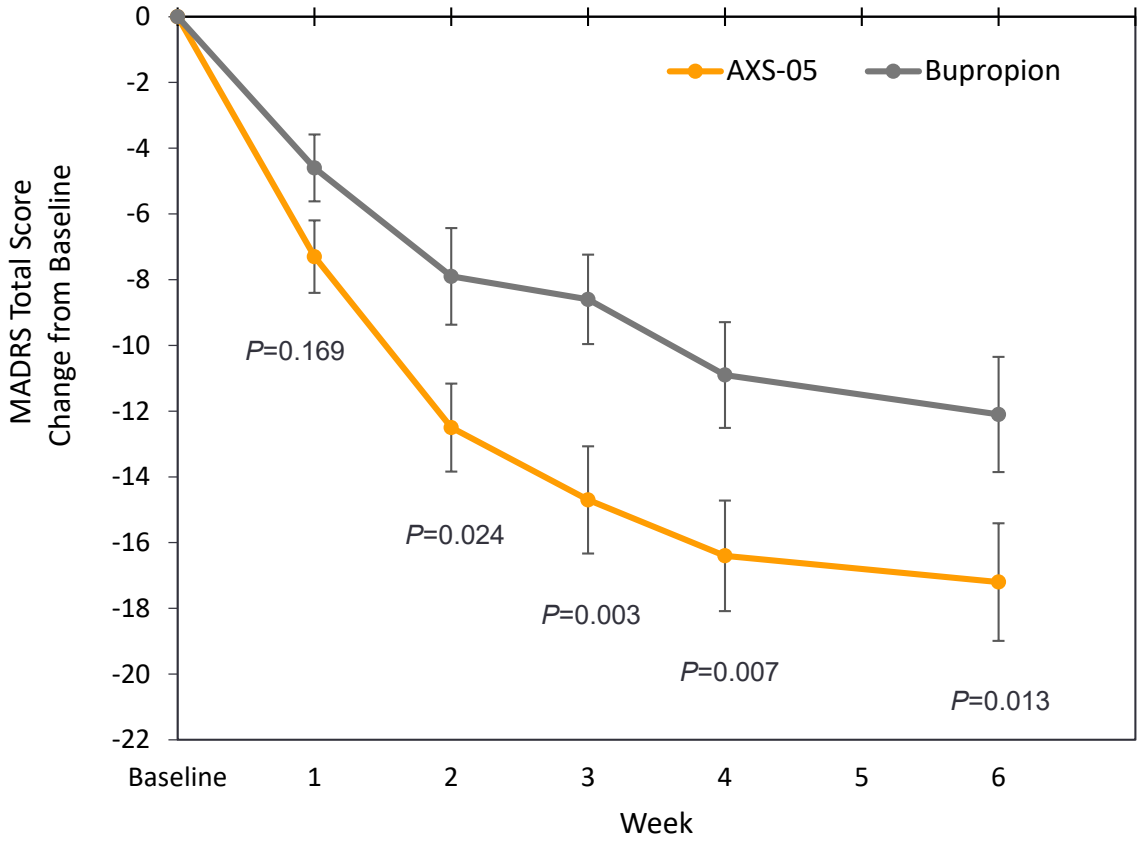
BUP = Bupropion; DM = Dextromethorphan

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

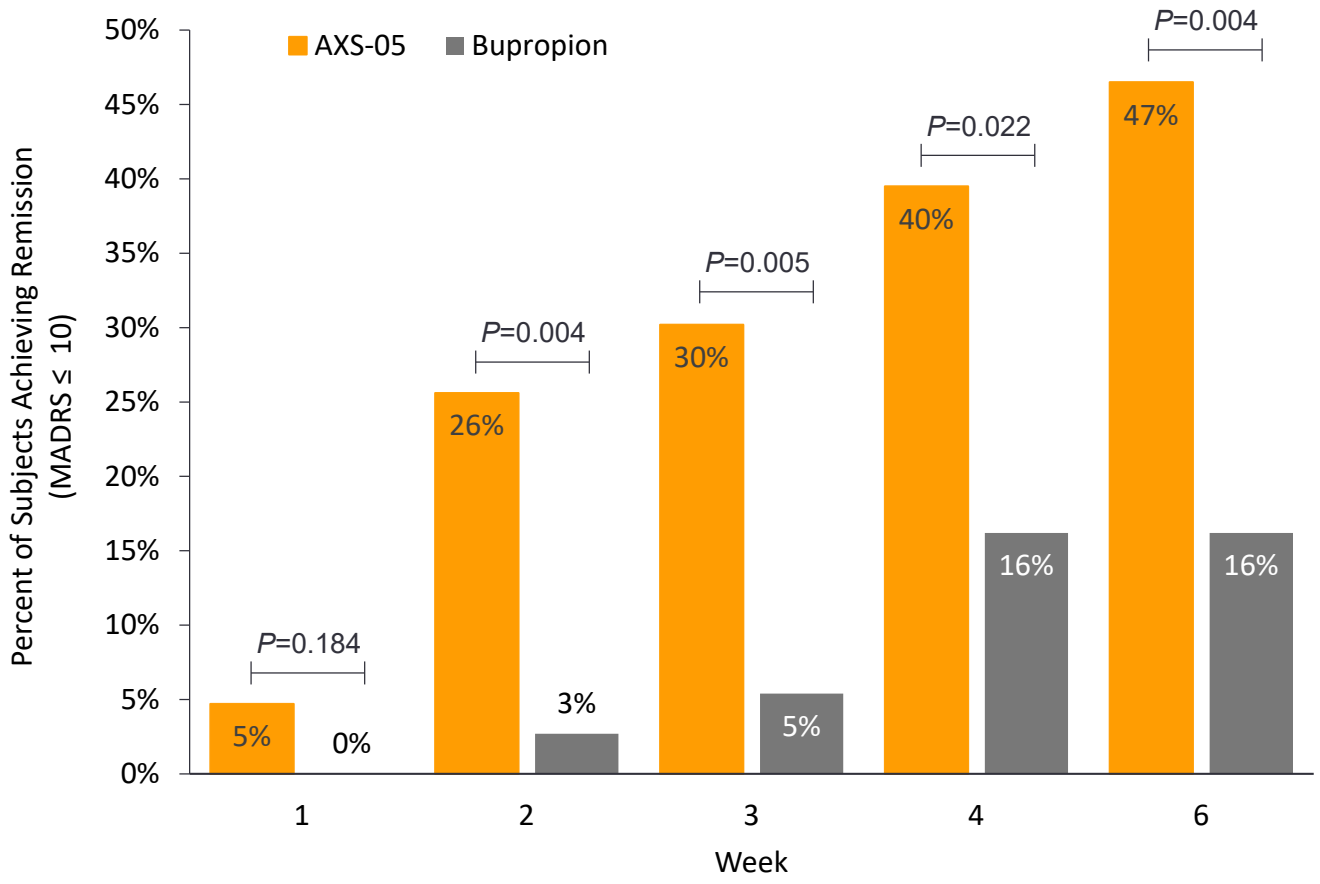
- Mean age (years): 37.3 for AXS-05 group, 37.7 for bupropion group
- Mean age at onset of illness (years): 26.5 for AXS-05 group, 26.6 for bupropion group
- Mean MADRS total score at baseline: 31.8 for AXS-05 group, 32.2 for bupropion group
- 51% of subjects had 3 or more major depressive episodes prior 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

ASCEND:
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 (≥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	0.038

* 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

AXSOME THERAPEUTICS

Chief Executive Officer
Axsome Therapeutics, Inc.

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**	● **STRIDE-1** top-line results (1Q 2019)
	AD Agitation	● **ADVANCE-1** interim efficacy analysis ● **ADVANCE-1** top-line results (2H 2019/1H 2020)
	MDD	✓ **ASCEND** top-line results
	Smoking Cessation	● **Ph 2** top-line results (1Q 2019)
AXS-07 (MoSEIC™ Mx + Riz)	**Migraine**	● **Ph 3** trial start (1Q 2019) ● **Ph 3** top-line results
AXS-12 (Reboxetine)	**Narcolepsy**	● **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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