NASDAQ: AXSM

AXSOME THERAPEUTICS

GEMINI Phase 3 Trial of AXS-05 in MDD

Topline Results

Conference Call

December 16, 2019

AXS-05 in Major Depressive Disorder (MDD)
GEMINI Phase 3 Trial Topline Results

Introduction	**Mark Jacobson**, Senior Vice President, Operations
Overview and Summary	**Herriot Tabuteau, MD**, Chief Executive Officer
GEMINI Trial Design & Results	**Cedric O'Gorman, MD**, Senior Vice President, Clinical Development & Medical Affairs
Q&A	**Presenters, Nick Pizzie**, Chief Financial Officer and **Dave Marek,** Chief Commercial 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.

Summary of Topline Results:
Rapid and Durable Effects with AXS-05

- 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

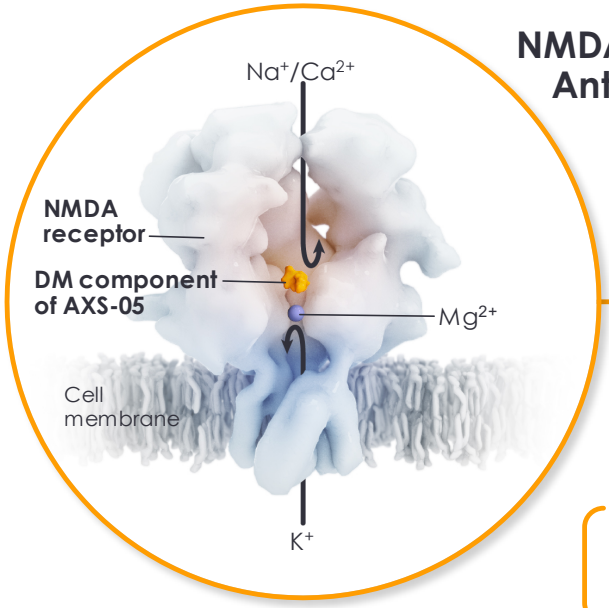
Major Depressive Disorder (MDD): Need for New, Innovative Treatments

- 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[2]
- 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[1]

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

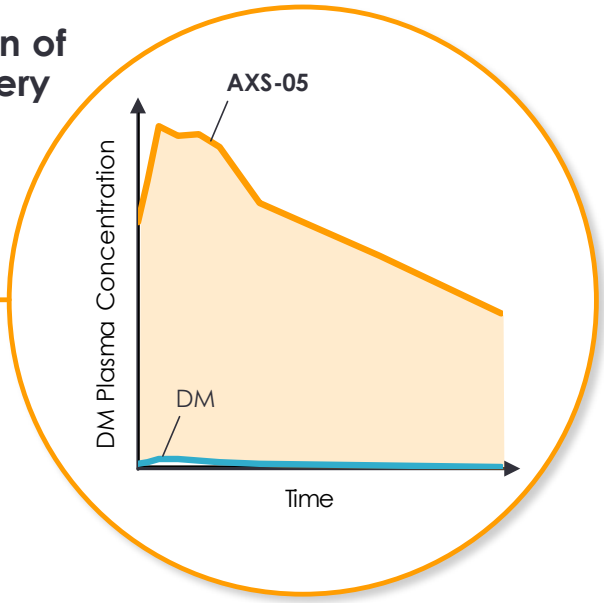


NMDA Receptor Antagonism

AXS-05

dextromethorphan/bupropion **modulated delivery tablet**

Modulation of DM Delivery



Sigma-1 Receptor Agonism

Monoamine Reuptake Inhibition

Abbreviations: DM = Dextromethorphan; Mg2+=magnesium ion; Na+=sodium ion; Ca+2=calcium ion; K+=potassium ion. Axsome data on file

GEMINI Phase 3 Trial Design & Results

Cedric O'Gorman MD, MBA

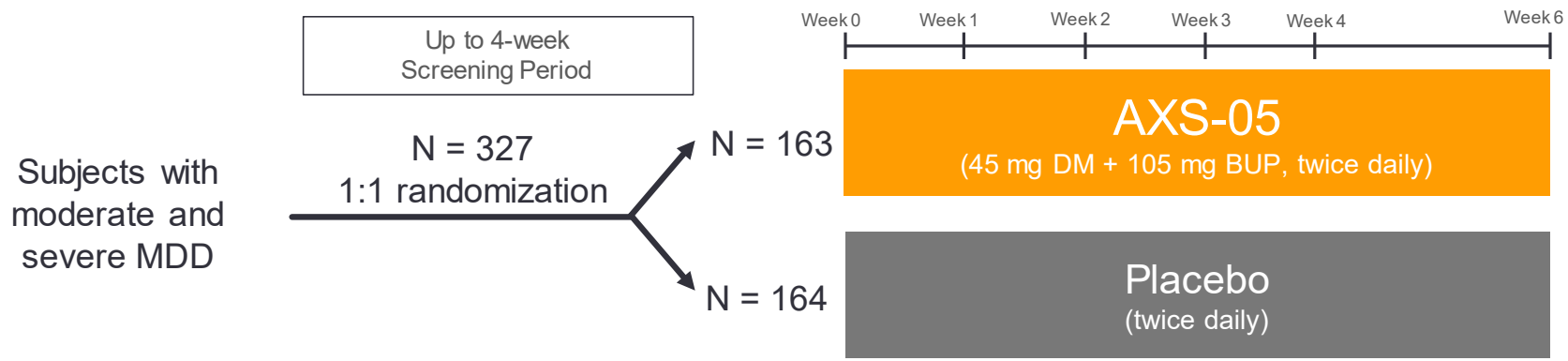
AXSOME THERAPEUTICS

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

GEMINI Phase 3 Trial: Design Summary

GEMINI STUDY

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 (≤10) at Week 6; MADRS response (≥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)

GEMINI Phase 3 Trial:
Key Entry Criteria

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 ≥ 25
- CGI-S score of ≥ 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

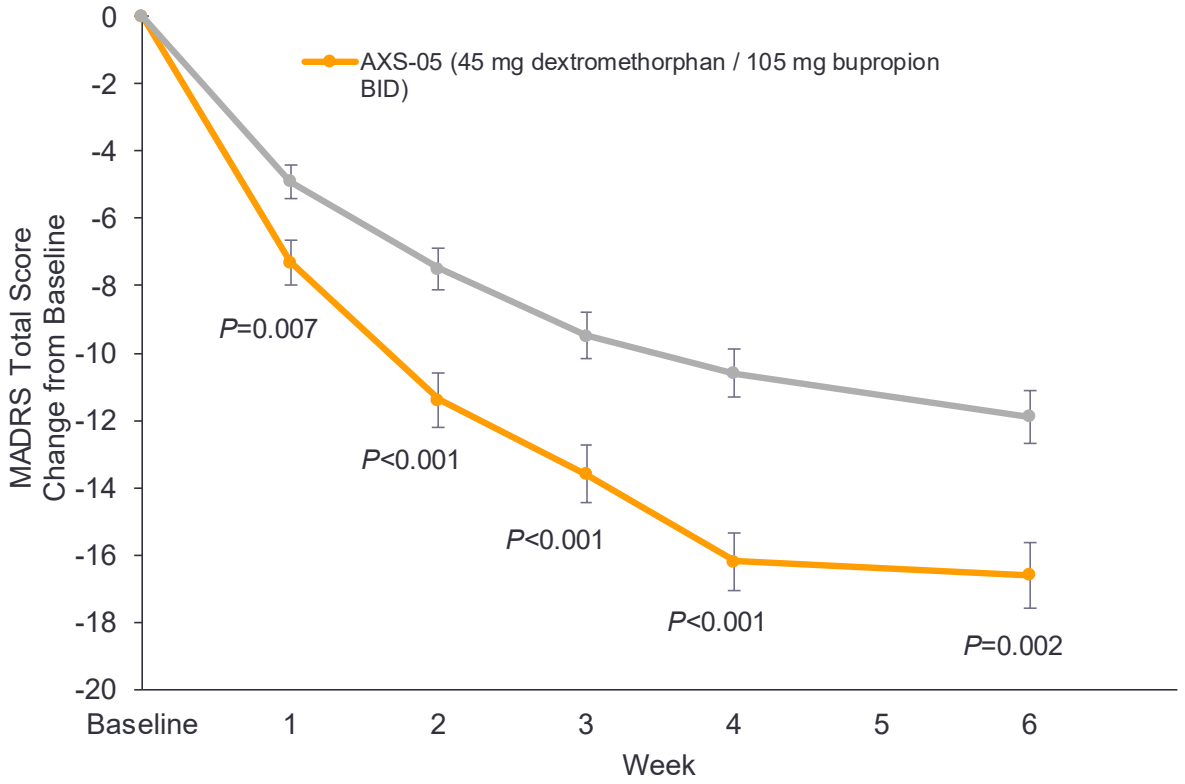
GEMINI Phase 3 Trial:
Demographics and Baseline Characteristics

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

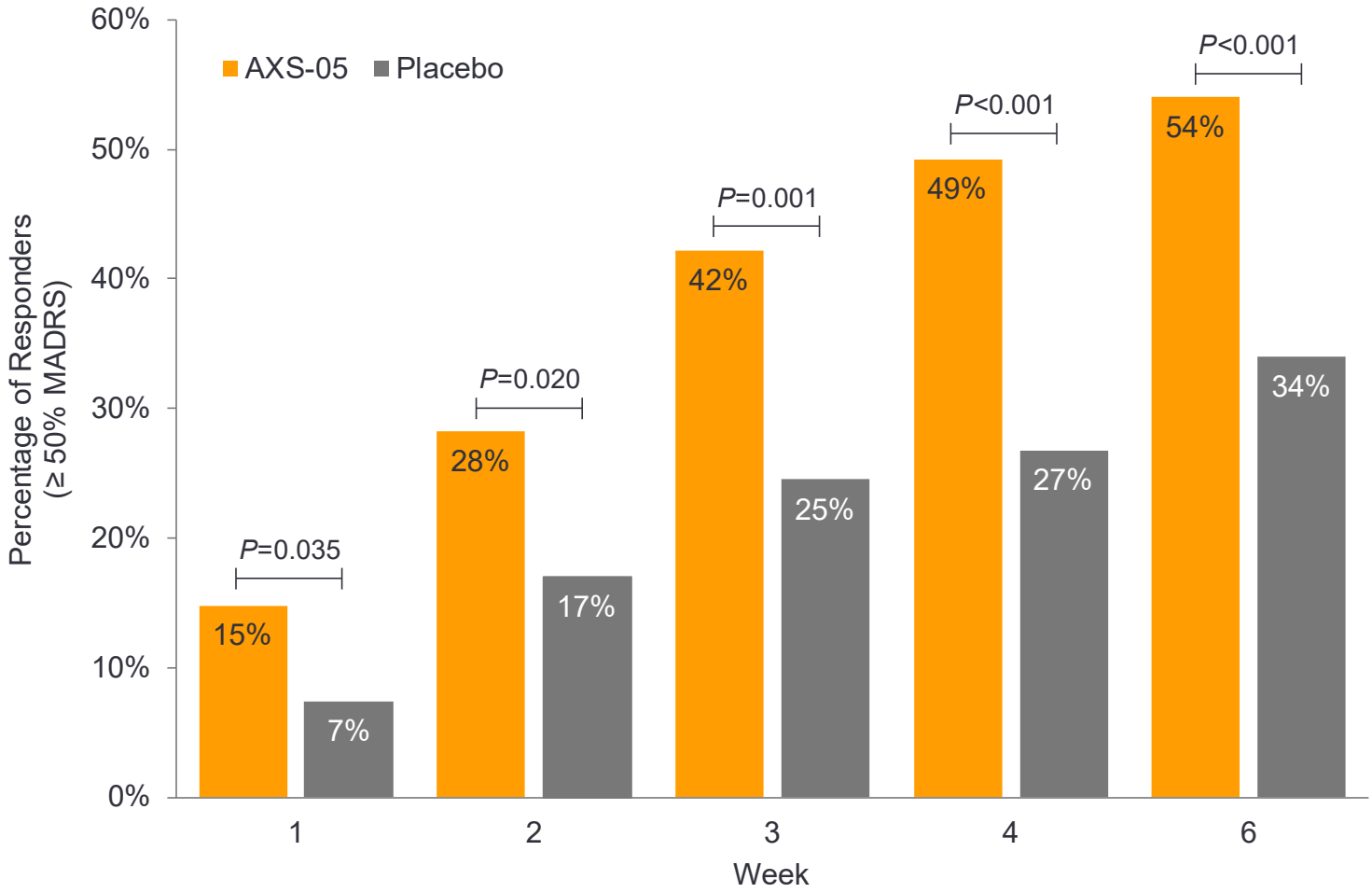
Improvement in Depressive Symptoms: Primary Endpoint – Change in MADRS Total Score



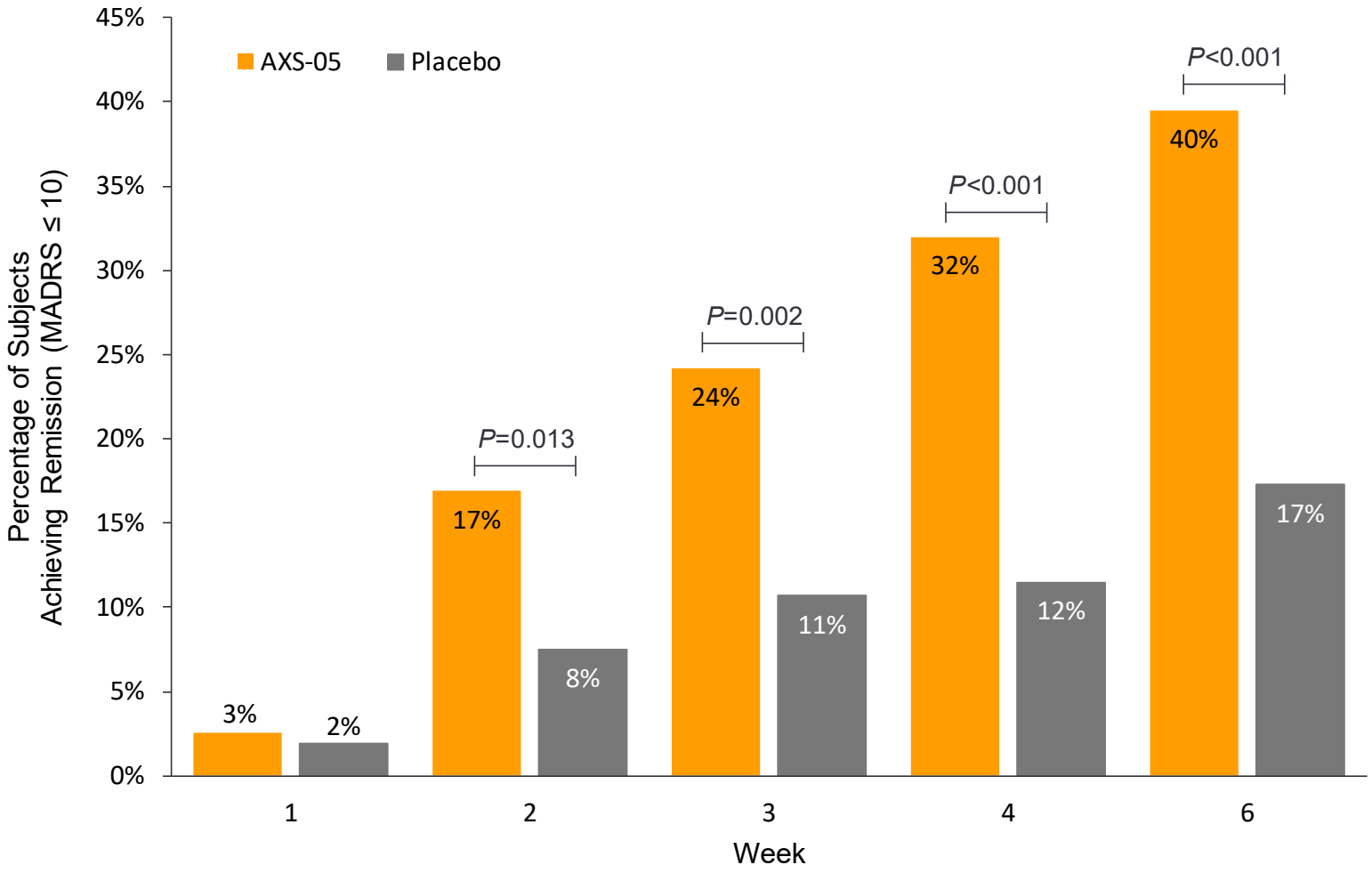
	AXS-05 (n=156)	Placebo (n=162)	Difference	*P*-Value
Primary Endpoint				
Change in MADRS Total Score at Week 6	-16.6	-11.9	-4.7	0.002
Key Secondary Endpoint				
Change in MADRS Total Score at Week 1	-7.3	-4.9	-2.4	0.007

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

Improvement in Depressive Symptoms: Clinical Response (≥ 50% MADRS improvement)



Improvement in Depressive Symptoms: Achievement of Remission (MADRS ≤ 10)



Rapid and Durable Improvements: Treatment Effects with AXS-05

	P-value		
	Week 1	**Week 2**	**Week 6**
Depressive Symptom Improvement			
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
Quality of Life and Functional Improvement			
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 ≥5% of Subjects

	AXS-05 (N = 162)	Placebo (N = 164)
Any Treatment-Emergent AE	**100 (61.7%)**	**74 (45.1%)**
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

- 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

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Concluding Remarks

Herriot Tabuteau, MD

Chief Executive Officer
Axsome Therapeutics, Inc.

AXS-05:
Clinical Programs in Psychiatry

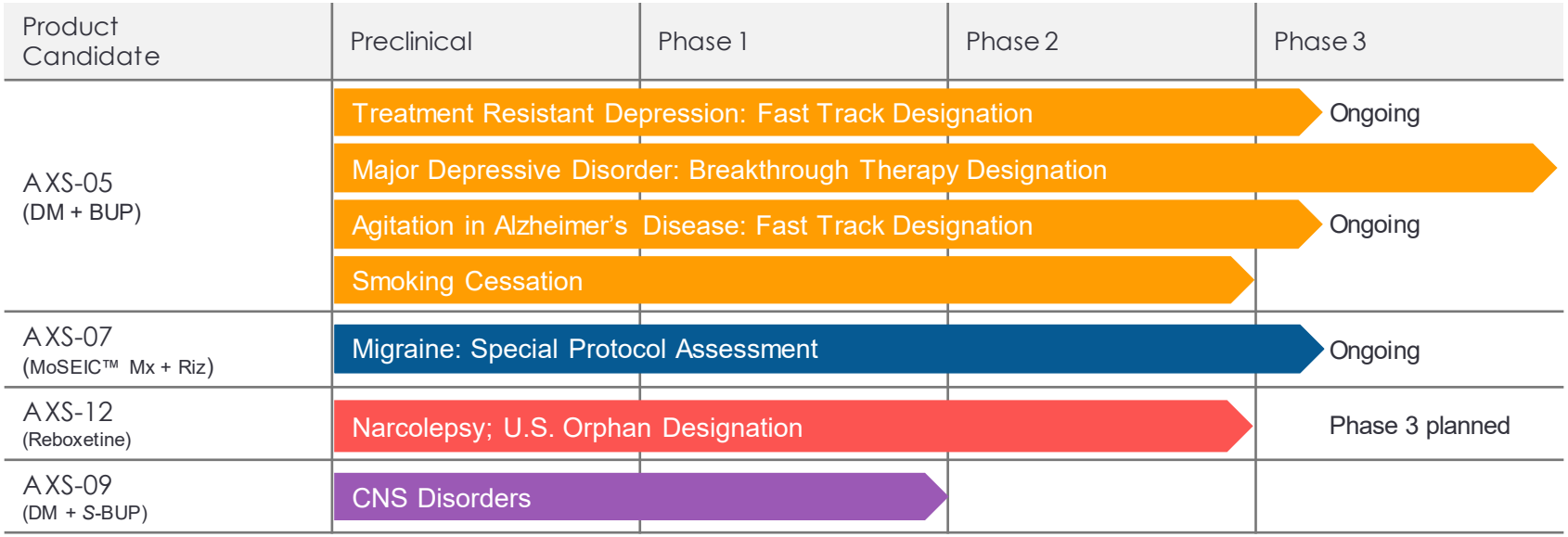
	Clinical Program				
	ASCEND	**GEMINI**	**STRIDE-1**	**AXS-05 / OL**	**ADVANCE-1**
Indication	MDD	MDD	TRD	MDD/TRD	Alzheimer's Agitation
Phase	Pivotal Phase 2	Pivotal Phase 3	Pivotal Phase 3	Open-label Phase 3	Pivotal Phase 2/3
Objectives	Efficacy of AXS-05 vs. BUP	Efficacy of AXS-05 vs. PBO	Efficacy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



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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