Auvelity® (AXS-05) in Major Depressive Disorder: Pooled Data from Two Six-Week Controlled Trials (GEMINI and ASCEND)

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Key Objectives

- Assess comprehensive efficacy and safety data from two pivotal randomized controlled trials of AXS-05 in MDD
- Determine if symptom improvement is affected by factors of prior antidepressant therapy, patient sex, and patient race
- Characterize the most frequently reported treatment-related adverse events, including time of onset and median duration

Conclusions

- Patients receiving AXS-05 demonstrated significantly improved depressive symptoms compared to the control population
  - Efficacy was consistent across patients irrespective of prior antidepressant treatment use in the current major depressive episode, patient sex, and patient race
- Most of the treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients treated with AXS-05 were reported within the first week; each of these resolved with a median duration between 2.5 and 16 days

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Disclosures

C. Chepke has participated in advisor boards for AbbVie, Acadia, Alkermes, Axsome Therapeutics, Biogen, Corium, Idorsia, Intra-Cellular, Janssen, Karuna, Lundbeck, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Teva; he has served as a consultant for AbbVie, Acadia, Alkermes, Axsome Therapeutics, Biogen, Boehringer Ingelheim, Corium, Intra-Cellular, Janssen, Karuna, Lundbeck, MedinCell, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Teva; he has served on a speaker's bureau with AbbVie, Acadia, Alkermes, Axsome, Corium, Intra-Cellular, Janssen, Karuna, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sumitomo, Teva; has as received research grant support from Acadia, Axsome, Harmony, Neurocrine, Teva. **D. Iosifescu** has received consulting honoraria from Alkermes, Allergan, Axsome Therapeutics, Biogen, Centers for Psychiatric Excellence, Jazz, Lundbeck, Otsuka, Precision Neuroscience, Sage, Sunovion; he has received research support (through his academic institutions) from Alkermes, Astra Zeneca, Brainsway, Litecure, Neosync, Otsuka, Roche, Shire. **G. ML. Eglit, C. Streicher,** and **H. Tabuteau** are current employees of Axsome Therapeutics.

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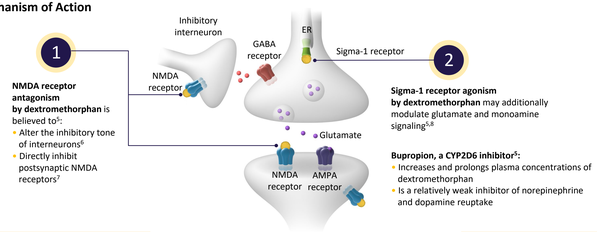
Introduction

- Differences in treatment response have been observed for patients with major depressive disorder by number of prior antidepressant therapies, sex, and race[1-3]
- Alongside these treatment response variations, many individuals experience enduring and burdensome tolerability problems associated with common antidepressant therapies[4]

AXS-05: An Oral NMDA Receptor Antagonist with Multimodal Activity

- AXS-05 ([dextromethorphan-bupropion] extended release tablet; AUVELITY) is a novel, oral, N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist, and aminoketone CYP2D6 inhibitor approved by the US Food and Drug Administration for the treatment of MDD in adults (**Figure 1**)[5]
  - Dextromethorphan is an NMDA receptor antagonist and a sigma-1 receptor agonist.[7]
  - Bupropion primarily serves to increase plasma concentrations and extend the half-life of dextromethorphan.[7]

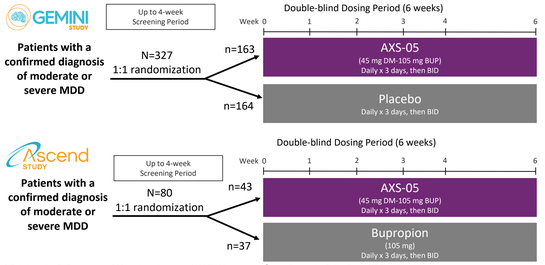
Figure 1. AXS-05 Mechanism of Action



Methods & Study Design

GEMINI and ASCEND

- The GEMINI pivotal phase 3 and ASCEND phase 2 trials assessed efficacy, tolerability, and safety of AXS-05 vs placebo or active control bupropion (BUP 105 mg), respectively, in patients with moderate to severe major depressive disorder[9,10]



BID, twice-daily; BUP, bupropion; DM, dextromethorphan; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder.

GEMINI Efficacy Outcomes

- Primary endpoint: change from baseline to Week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score
- Other efficacy endpoints: change from baseline in the MADRS total score at Week 1; change from baseline in the MADRS total score at Week 2; remission, defined as MADRS total score ≤ 10, at Week 2; and clinical response, defined as ≥ 50% reduction in MADRS total score, at Week 6

ASCEND Efficacy Outcomes

- Primary endpoint: average change from baseline in MADRS Total Score for Weeks 1-6
- Other efficacy endpoints: change from baseline in the MADRS total score at Week 6; change from baseline in the MADRS total score at Week 1; change from baseline in the MADRS total score at Week 2; remission, defined as MADRS total score ≤ 10

Table 1. GEMINI and ASCEND Key Inclusion / Exclusion Criteria

Inclusion	Exclusion
• Male or female 18-65 years of age • Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for current major depressive disorder without psychotic features • Montgomery-Åsberg Depression Rating Scale total score of ≥25 • Clinical Global Impressions-Severity score of ≥4 at baseline	• History of depressive episode with psychotic or catatonic features, treatment-resistant depression (defined as 2 or more failed prior treatments of adequate dose and duration in the current depressive episode), schizophrenia, bipolar disorder, panic disorder, obsessive convulsive disorder, bulimia or anorexia nervosa, persistent neurocognitive disorder, or primary anxiety disorder • Alcohol/substance use disorder within 1-year • Clinically significant risk of suicide or harm to self or others • Seizure disorder • Concomitant psychotropic medication

MADRS; Montgomery-Åsberg Depression Rating Scale; CGI-S, Clinical Global Impressions-Severity .

- GEMINI and ASCEND data were pooled, with placebo and bupropion arms combined into a Control arm in this post hoc analysis
- Efficacy was measured as change from baseline on the Montgomery-Åsberg Depression Rating Scale (MADRS) among participants stratified by prior antidepressant treatment (ADT) use in the current major depressive episode, sex, and race
- Safety analyses quantified timing of treatment emergent adverse event (TEAE) onset and duration of TEAEs

Key Findings

Patient Population

Table 2. Demographics and Baseline Characteristics (Safety Population)

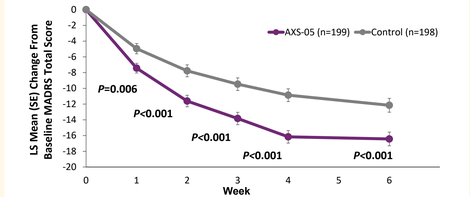
	AXS-05 (n=210)	Control (n=212)
Mean Age (SD), years	41.2 (12.67)	40.6 (13.54)
Female Sex, n (%)	125 (59.5)	149 (70.3)
Number of Prior ADTs, n (%)		
=0	166 (79.0)	148 (69.8)
≥1	44 (21.0)	64 (30.2)
Race, n (%)		
White	119 (57.8)	120 (60.0)
Non-White	87 (42.2)	80 (40.0)
Mean Baseline BMI (SD), kg/m²	29.2 (5.66)	29.4 (5.55)
Mean Baseline MADRS total score (SD)	33.2 (4.40)	33.0 (4.37)

ADT, antidepressant therapies; BMI, body mass index; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation.

- Baseline and sociodemographic characteristics were generally similar across AXS-05 and Control groups (**Table 2**)

Efficacy

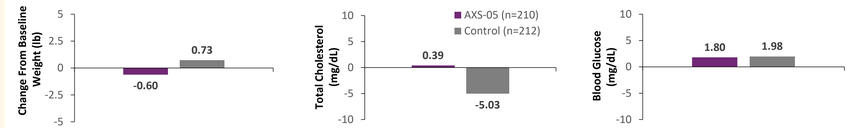
Figure 2. MADRS Total Score Change from Baseline



- AXS-05 exhibited consistent efficacy in observed subgroups:
  - **Prior ADT (antidepressant therapy):** AXS-05 significantly reduced MADRS total score from baseline compared to control starting from Week 1 irrespective of prior ADT (Week 1: *P*=0.032 without prior ADT and *P*=0.015 with ≥1 prior ADT)
  - **Sex:** AXS-05 significantly reduced MADRS total score from baseline compared to control starting from Week 2 irrespective of sex (Week 6: *P*=0.007 for females and *P*=0.009 for males)
  - **Race:** AXS-05 significantly reduced MADRS total score from baseline compared to control starting from Week 4 irrespective of race (Week 6: *P*=0.005 for white patients and *P*=0.020 for non-white patients)

Select Metabolic Measures

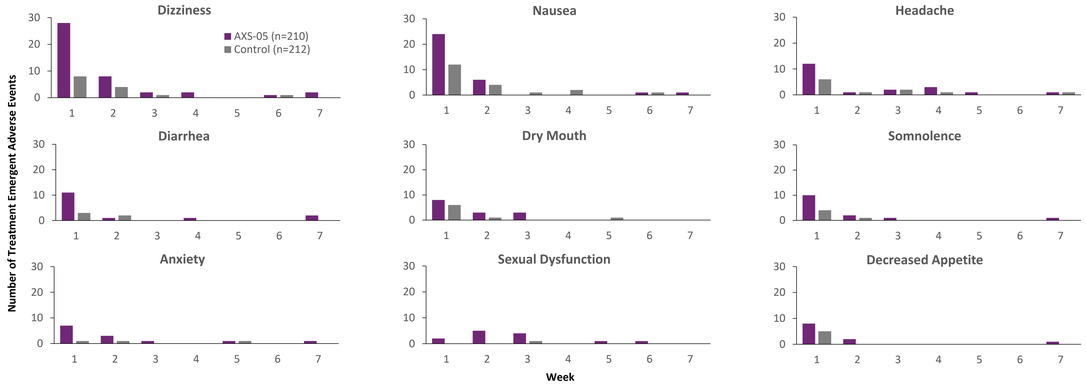
Figure 3. Summary of Change from Baseline at Week 6 in Weight (A), Total Cholesterol (B), and Blood Glucose (C)



- No substantial changes were observed in weight, total cholesterol, or blood glucose between baseline and Week 6 (**Figure 3**)

Safety

Figure 4. Onset of Treatment Emergent Adverse Events in ≥5% of Participants Treated With AXS-05



[a]The data includes all incidences, including multiple incidences for individual patients.

- Most incidences of TEAEs in ≥5% of AXS-05 patients were reported in Week 1 and resolved with a median duration of 2.5-16 days (**Figure 4 and Table 3**)

Table 3. Summary of Frequency and Median Duration of Treatment Emergent Adverse Events in ≥5% of Participants Treated With AXS-05

	AXS-05 (n=210)		Control (n=212)	
	n (%)	Median Duration (Days/Event[a])	n (%)	Median Duration (Days/Event[a])
Dizziness	36 (17.1)	5	12 (5.7)	12
Nausea	29 (13.8)	6	20 (9.4)	4.5
Headache	17 (8.1)	2.5	11 (5.2)	6
Diarrhea	14 (6.7)	4	5 (2.4)	8
Dry mouth	14 (6.7)	12.5	8 (3.8)	12
Somnolence	12 (5.7)	5	5 (2.4)	12
Anxiety	12 (5.7)	7	3 (1.4)	2
Sexual Dysfunction[b]	11 (5.2)	3	1 (0.5)	26
Decreased appetite	11 (5.2)	16	5 (2.4)	12

[a]The data includes all incidences, including multiple incidences for individual patients. [b]Includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia.