AXS-05 (Auvelity®) 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

References

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Disclosures

C. Chepke has participated in advisor boards for AbbVie, Acadia, Alkermes, Axsome, 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, 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, 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. Eglit, C. Streicher**, and **H. Tabuteau** are current employees of Axsome Therapeutics.

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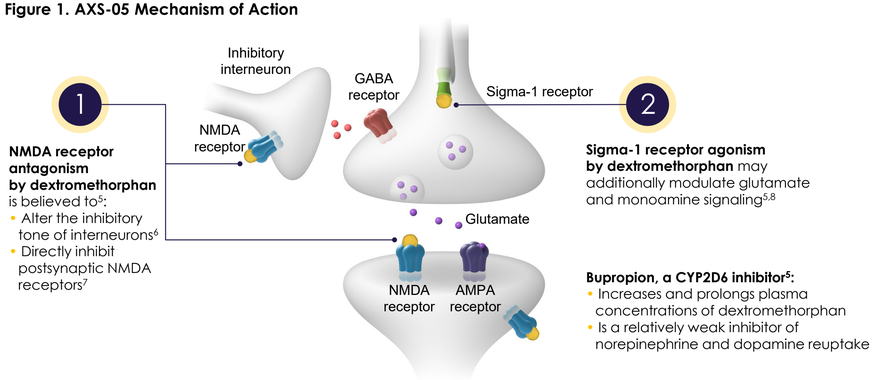
Introduction

- 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 a NMDA receptor antagonist and a sigma-1 receptor agonist[5]
  - Bupropion primarily serves to increase plasma concentrations and extend the half-life of dextromethorphan[5]

Figure 1. AXS-05 Mechanism of Action



NMDA receptor antagonism by dextromethorphan is believed to[5]:
- Alter the inhibitory tone of interneurons[6]
- Directly inhibit postsynaptic NMDA receptors[7]

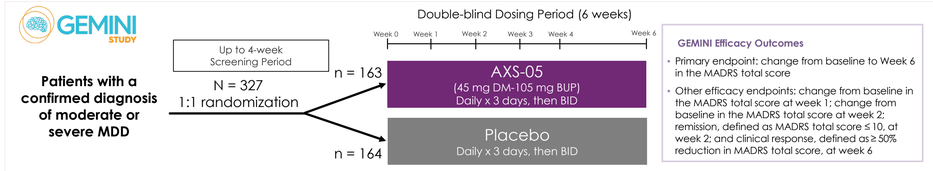
Sigma-1 receptor agonism by dextromethorphan may additionally modulate glutamate and monoamine signaling[5,8]

Bupropion, a CYP2D6 inhibitor[5]:
- Increases and prolongs plasma concentrations of dextromethorphan
- Is a relatively weak inhibitor of norepinephrine and dopamine reuptake

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.

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

- 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)

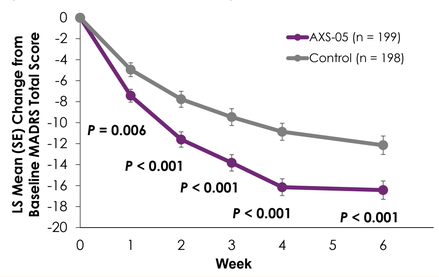
	AXS-05 (n = 210)	Control (n = 212)
Mean age (SD), years	41.2 (12.67)	40.6 (13.54)
Female Sex, n (%)	125 (59.5)	149 (70.3)
Number of Prior ADTs, n (%)		
= 0	166 (79.0)	148 (69.8)
≥ 1	44 (21.0)	64 (30.2)
Race, n (%)		
White	119 (57.8)	120 (60.0)
Non-White	87 (42.2)	80 (40.0)
Mean baseline BMI (SD), kg/m²	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

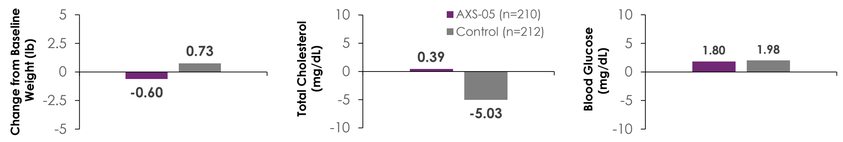
Figure 2. MADRS Total Score Change from Baseline



- 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

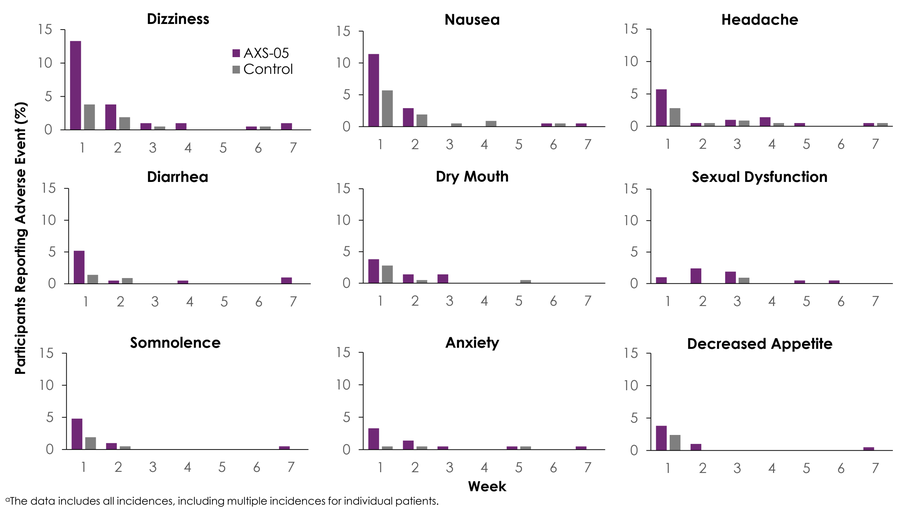
Figure 3. Summary of Change from Baseline at Week 6 in Weight (A), Total Cholesterol (B), and Blood Glucose (C)



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

Safety

Figure 4. Incidences[a] of TEAEs by Adverse Event Start Date and Preferred Term



[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 Median Duration of Treatment Emergent Adverse Events by Preferred Term

	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 (2.3)	8
Dry mouth	14 (6.7)	12.5	8 (3.8)	12
Sexual dysfunction	12 (5.7)	3	2 (0.9)	18.5
Somnolence	12 (5.7)	5	5 (2.4)	12
Anxiety	12 (5.7)	7	3 (1.4)	2
Decreased appetite	11 (5.2)	16	5 (2.4)	12

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