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 pooled safety and efficacy data from two pivotal randomized controlled trials of AXS-05 in MDD.
- Characterize details of the most frequently reported treatment-emergent adverse events (TEAEs) occurring in AXS-05, including incidence, duration, onset, and absolute prevalence.
- Evaluate if symptom improvement is affected by factors of participant sex, race, and presence or absence of prior antidepressant therapy (ADT).

Conclusions

- Findings were consistent with previously-reported trials and support the early occurrence and resolution of the most common TEAEs associated with AXS-05.
- The most common TEAEs reported in the pooled AXS-05 population were dizziness (17.1%), nausea (13.8%), and headache (8.1%); all TEAEs reported in ≥ 5% of AXS-05 participants resolved with a median duration of 2.5 days to 16 days.
- Of the TEAEs reported in ≥ 5% of participants treated with AXS-05, most incidences were reported in the first 7 days, and the absolute prevalence ranged from 1.8% to 6.1%.
- Efficacy of AXS-05 was comparable among participants differing in sex (male vs. female), race (white vs. non-white), and presence or absence of prior antidepressant therapy (ADT).

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Acknowledgments

This study was funded by Axsome Therapeutics. Under the direction of the authors, Daniel Roybal, PhD, of Axsome Therapeutics, Inc., provided medical writing and editorial support for this poster

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, and 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, and 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, and Teva; has received research grant support from Acadia, Axsome, Harmony, Neurocrine, and Teva. **D. Iosifescu** has received consulting honoraria from Alkermes, Allergan, Autobahn, Axsome Therapeutics, Biogen, Boehringer Ingelheim, Centers for Psychiatric Excellence, Cleveo, Delix, Jazz, Lundbeck, Neumora, Otsuka, Precision Neuroscience, Relmada, Sage, and Sunovion; he has received research support (through his academic institutions) from Alkermes, Astra Zeneca, Brainsway, Litecure, Neosync, Otsuka, Roche, and Shire. **G. Eglit, C. Streicher, S. Alter** and **H. Tabuteau** are current employees of Axsome Therapeutics.

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NEI Congress
November 7-10, 2024, Colorado Springs, CO

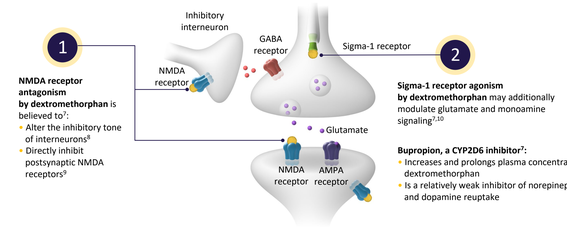
Introduction

- Major depressive disorder (MDD) is a debilitating condition that affects approximately 1 in 5 people in the United States over their lifetime.[1]
- Despite the availability of dozens of antidepressant therapies (ADTs), many patients with MDD experience enduring and burdensome side effects associated with the traditionally-used ADTs.[2,3]
- Up to 25% of patients discontinue their ADT due to intolerable side effects, leading to poor treatment outcomes.[4]
- In the GEMINI and ASCEND trials, AXS-05 demonstrated a well-tolerated safety profile characterized by generally manageable adverse events and low rates of discontinuations.[5,6]
- Understanding the duration, onset, and prevalence of adverse events may help healthcare providers manage patient expectations and strengthen shared decision-making to ultimately improve treatment adherence.
- Furthermore, ADTs that demonstrate consistent improvement in depressive symptoms across patient demographics may assure treatment choices.

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

- Auvelity (AXS-05; dextromethorphan-bupropion extended-release tablet) 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**).[7]
  - Dextromethorphan is an NMDA receptor antagonist and a sigma-1 receptor agonist.[7]
    - The antidepressant effect of dextromethorphan is thought to involve reducing GABA-mediated inhibition of glutamate release and shifting synaptic glutamate signaling towards postsynaptic AMPA over NMDA receptors.[8,9]
  - Bupropion primarily serves to increase plasma concentrations and extend the half-life of dextromethorphan.[7]

Figure 1. AXS-05 Mechanism of Action



NMDA receptor antagonism by dextromethorphan is believed to[7]:
- Alter the inhibitory tone of interneurons[8]
- Directly inhibit postsynaptic NMDA receptors[9]

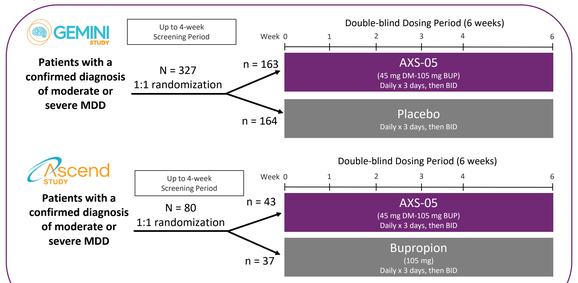
Sigma-1 receptor agonism by dextromethorphan may additionally modulate glutamate and monoamine signaling[7,10]

Bupropion, a CYP2D6 inhibitor[7]:
- 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 Phase 3 and ASCEND Phase 2 studies assessed efficacy, tolerability, and safety of AXS-05 vs active control bupropion (BUP 105 mg) or placebo, respectively, in participants with moderate to severe major depressive disorder.[5,6]



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

- GEMINI and ASCEND data were pooled to assess the safety and efficacy of AXS-05 on a broader scale.
- Safety analyses characterize the incidence, duration, onset, and absolute prevalence of the most common treatment-emergent adverse events (TEAEs) occurring in participants treated with AXS-05.
- Depression symptom improvement from baseline was assessed in subgroups stratified by participant sex, race, and prior use of an ADT in the current major depressive episode.
  - Placebo and bupropion populations from GEMINI and ASCEND, respectively, were pooled to represent a Control group for subgroup efficacy analyses.

Key Findings

Participant Population

Table 2. Demographics and Baseline Characteristics (Safety Population)

	AXS-05 (n = 210)	Placebo (n = 164)	Bupropion (105 mg BID; n = 48)
Mean age (SD), years	41.2 (12.67)	41.1 (13.78)	39.1 (12.72)
Female Sex, n (%)	125 (59.5)	117 (71.3)	32 (66.7)
Number of Prior ADTs, n (%)			
= 0	166 (79.0)	113 (68.9)	35 (72.9)
≥ 1	44 (21.0)	51 (31.1)	13 (27.1)
Race, n (%)			
White	119 (57.8)	92 (59.0)	28 (63.6)
Non-White	87 (42.2)	64 (41.0)	16 (36.4)
Mean baseline BMI (SD), kg/m²	29.2 (5.66)	29.4 (5.66)	29.6 (5.21)
Mean baseline MADRS total score (SD)	33.2 (4.54)	33.1 (4.36)	31.6 (4.25)

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

Safety Summary

Table 3. Overall Summary of Treatment-Emergent Adverse Events

n (%)	AXS-05 (n = 210)	Placebo (n = 164)	Bupropion (105 mg BID; n = 48)
Participants with any TEAE	135 (64.3)	75 (45.1)	31 (64.6)
Participants with serious TEAEs	1 (0.5)	0	0
Participants with severe TEAEs	4 (3.0)	2 (2.7)	1 (3.2)
Participants with TEAEs that led to drug withdrawn	16 (7.6)	1 (0.6)	6 (12.5)

BID, two times a day; TEAE, treatment-emergent adverse event.

Incidence and Duration of TEAEs

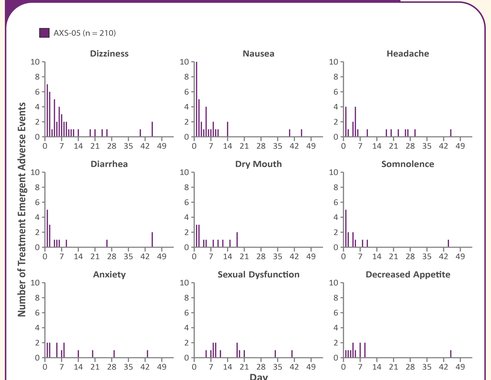
Table 4. Summary of Frequency and Median Duration of Treatment-Emergent Adverse Events Occurring in ≥ 5% of Participants Treated With AXS-05

	AXS-05 (n = 210)			Placebo (n = 164)			Bupropion (105 mg BID; n = 48)		
	n (%)	No. of Events[a]	Median Duration[b] (IQR)	n (%)	No. of Events[a]	Median Duration[b] (IQR)	n (%)	No. of Events[a]	Median Duration[b] (IQR)
Dizziness	36 (17.1)	43	5 (1-15.5)	10 (6.1)	12	14.5 (8.75-18.25)	2 (4.2)	2	3.5 (3.25-3.75)
Nausea	29 (13.8)	32	6 (2.75-9)	14 (8.5)	14	8.5 (3.25-14.75)	6 (12.5)	6	1.5 (1-3.5)
Headache	17 (8.1)	20	2.5 (1.75-10.5)	6 (3.7)	6	2.5 (1-13)	5 (10.4)	5	14 (6-26)
Diarrhea	14 (6.7)	15	4 (2.5-11)	5 (3.0)	5	8 (1-11)	0	0	-
Dry mouth	14 (6.7)	14	12.5 (4.5-33)	4 (2.4)	4	12 (9.25-12.5)	4 (8.3)	4	14.5 (9.75-32.5)
Somnolence	12 (5.7)	13	5 (3-14)	5 (3.0)	5	12 (1-15)	0	0	-
Anxiety	12 (5.7)	13	7 (2-18)	2 (1.2)	2	20 (10.5-29.5)	1 (2.1)	1	2 (2-2)
Sexual dysfunction[c]	11 (5.2)	13	3 (1-14)	0	0	-	1 (2.1)	1	26 (26-26)
Decreased appetite	11 (5.2)	11	16 (9.5-46.5)	1 (0.6)	1	30 (30-30)	4 (8.3)	4	11 (7.75-12.5)

BID; two times a day; IQR, interquartile range.
[a]Includes all incidences, including multiple incidences for individual participants. [b]Days/event. [c]Includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia.

Onset of TEAEs

Figure 2. Onset of Treatment-Emergent Adverse Events Occurring in ≥ 5% of Participants Treated With AXS-05



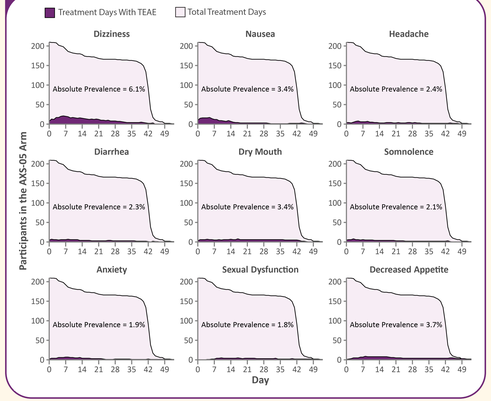
The data includes all incidences, including multiple incidences for individual participants.

- More TEAE onsets occurred during the first week of treatment compared to each subsequent week for each TEAE except for sexual dysfunction.
- Additionally, there were more TEAE onsets occurring during the first seven days of treatment compared to all subsequent days together for each TEAE except for sexual dysfunction.
- For sexual dysfunction, there were 2 events with an onset during the first week and 5 with an onset during the second week.

Absolute Prevalence of TEAEs

- The absolute prevalence of dizziness in the AXS-05 group was 6.1% (n = 461/7516), meaning that 461 participant treatment days had this TEAE out of the 7516 participant treatment days in which this TEAE could have occured.
- The absolute prevalence of the other common TEAEs were as follows: nausea (3.4%, n = 252/7516); headache (2.4%, n = 177/7516); diarrhea (2.3%, n = 172/7516); dry mouth (3.4%, n = 259/7516), anxiety (1.9%, n = 141/7516), somnolence (2.1%, n = 156/7516), sexual dysfunction (1.8%, n = 136/7516), and decreased appetite (3.7%, n = 280/7516).

Figure 3. Absolute Prevalence of Treatment-Emergent Adverse Events Occurring in ≥ 5% of Participants Treated With AXS-05



Subgroup Efficacy

Figure 4. Subgroup Analysis of MADRS Change from Baseline Least Square Mean Difference from Control at Weeks 1, 2, and 6

Week	Subgroup	AXS-05	Control	Least-Square Mean Difference from Control in MADRS change from Baseline (95% CI)
Week 1				
	Sex			
	Female	120	143	-2.42 (-4.24 to -0.61)
	Male	79	55	-1.85 (-4.22 to 0.53)
	Race			
	White	114	111	-2.48 (-4.36 to -0.61)
	Non-White	81	77	-2.06 (-4.44 to 0.31)
	Prior ADT			
	No Prior ADT	155	134	-1.83 (-3.51 to -0.15)
	Prior ADT	44	64	-3.46 (-6.24 to -0.68)
Week 2				
	Sex			
	Female	120	143	-3.58 (-5.85 to -1.31)
	Male	79	55	-3.77 (-6.81 to -0.74)
	Race			
	White	114	111	-4.56 (-6.90 to -2.21)
	Non-White	81	77	-2.53 (-5.53 to 0.46)
	Prior ADT			
	No Prior ADT	155	134	-3.61 (-5.76 to -1.46)
	Prior ADT	44	64	-3.57 (-6.92 to -0.21)
Week 6				
	Sex			
	Female	120	143	-3.85 (-6.65 to -1.05)
	Male	79	55	-4.88 (-8.53 to -1.23)
	Race			
	White	114	111	-4.15 (-7.01 to -1.28)
	Non-White	81	77	-4.35 (-8.00 to -0.70)
	Prior ADT			
	No Prior ADT	155	134	-3.73 (-6.33 to -1.13)
	Prior ADT	44	64	-4.36 (-8.63 to -0.09)

-10.0 -8.0 -6.0 -4.0 -2.0 0.0 2.0
AXS-05 Better — Control Better

- A larger MADRS change from baseline in the least square mean difference from Control was observed at Weeks 1, 2, and 6, indicating superiority of AXS-05 over placebo- and bupropion-treated participants in the Control group.
- Superiority versus Control was shown regardless of participant sex, race, and prior treatment with an ADT.