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 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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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 as 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, Clexio, 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**, and **H. Tabuteau** are current employees of Axsome Therapeutics.

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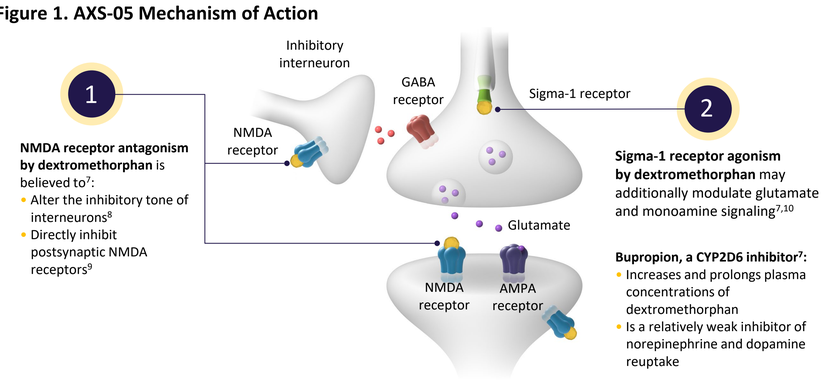
Introduction

- 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

- 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]

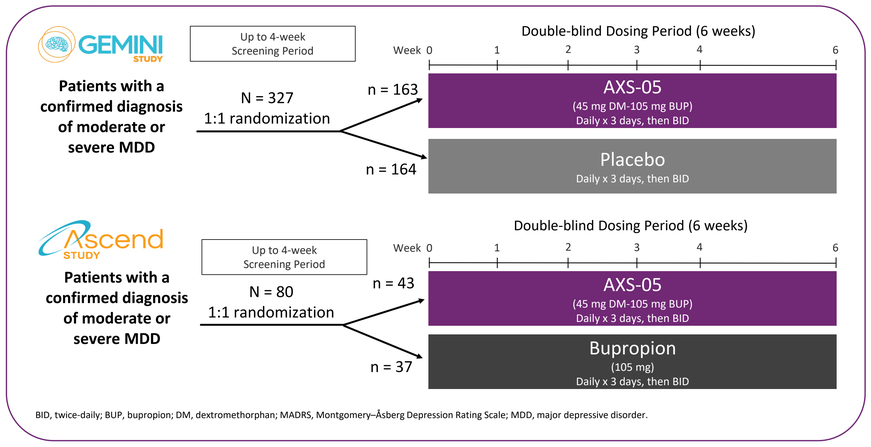
Figure 1. AXS-05 Mechanism of Action



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

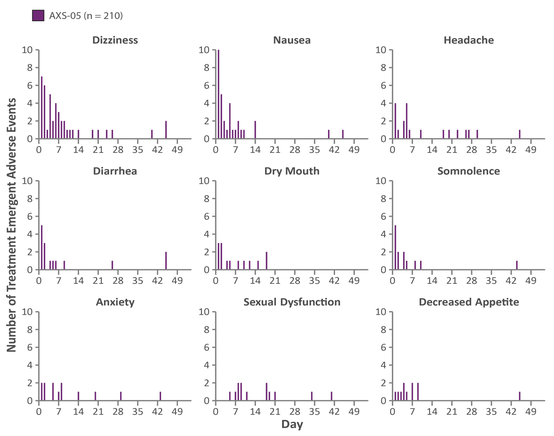
Table 4. Summary of Frequency and Median Duration of Treatment-Emergent Adverse Events Occurring in ≥ 5% of Participants Treated With AXS-05

	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



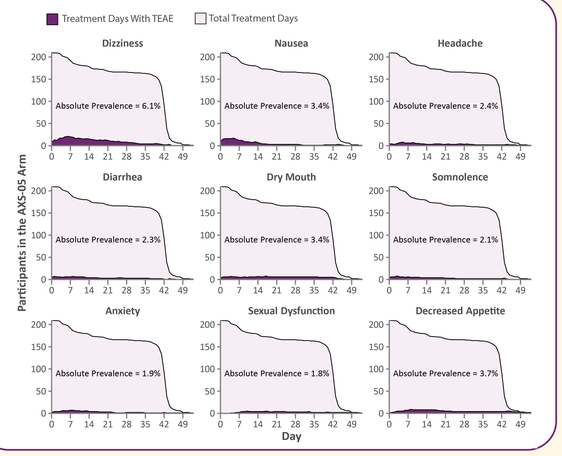
The data includes all incidences, including multiple incidences for individual participants.

- 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

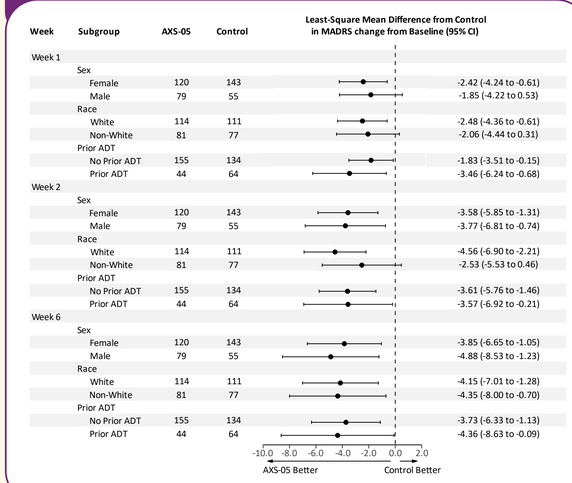
- The absolute prevalence of dizziness in the AXS-05 group was 6.1% (n = 461/7516), meaning that 461 participant treatment days had this TEAE out of the 7516 participant treatment days in which this TEAE could have occurred.
- The absolute prevalence of the other common TEAEs were as follows: nausea (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



- 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.