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Clinical Program Overview of AXS-05 in Psychiatric Conditions With High Unmet Needs

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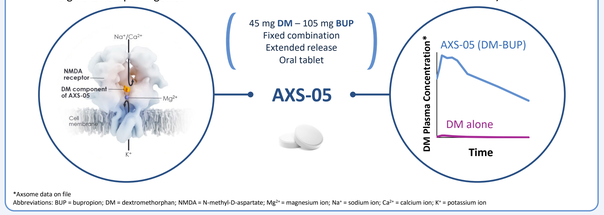
Objective

- Summarize the AXS-05 clinical development programs in two psychiatric conditions with high unmet need: major depressive disorder and Alzheimer's disease agitation

Introduction

- AXS-05 is formulated as an extended-release oral tablet containing a fixed dose combination of 45 mg dextromethorphan + 105 mg bupropion (DM-BUP; Auvelity®)[1,2]
- Rationale for combining dextromethorphan and bupropion is based on pharmacokinetic synergy:
  - Dextromethorphan is a compound that acts on receptors in the brain – an N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist – and is rapidly metabolized by the liver enzyme CYP2D6[1,2]
  - Bupropion is a CYP2D6 inhibitor[2,3]
  - Combined as AXS-05, bupropion allows dextromethorphan to reach therapeutically beneficial plasma and central nervous system (CNS) concentrations[4,5]

AXS-05 Mechanism of Action



*Axsome data on file
Abbreviations: BUP = bupropion; DM = dextromethorphan; NMDA = N-methyl-D-aspartate; Mg^{2+} = magnesium ion; Na^{+} = sodium ion; Ca^{2+} = calcium ion; K^{+} = potassium ion

- AXS-05 is thought to work by modulating the neurotransmission of glutamate, the brain's most abundant neurotransmitter, in addition to other mechanisms of action[1,2,6,7]
- Dextromethorphan-bupropion (Auvelity; AXS-05) was FDA-approved in adults with major depressive disorder (MDD) in 2022 and AXS-05 was granted FDA Breakthrough Therapy designation by the FDA for clinical development as a treatment for Alzheimer's disease agitation (AD agitation)*
- Approximately 70% of patients with Alzheimer's disease exhibit agitation characterized by both aggressive and non-aggressive behaviors[8,9]

* Dextromethorphan-bupropion (AXS-05) is not currently FDA-approved for use in AD agitation

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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, Litesure, Neosync, Otsuka, Roche, and Shire. **M Fava** has received research support, served as a consultant and on advisory board, received speaking/publishing awards, and owns stock or other financial options from and in a variety of companies and institutions; find his lifetime disclosures (updated Dec 2024) here – https://mghcme.org/maurizio-fava-bio-disclosure/
G Grossberg has provided consultation to Acadia, Alkahest, Avanir, Axsovant, Axsome Therapeutics, Biogen, BioXcel, Genentech, Karuna, Lundbeck, Otsuka, Roche, and Takeda. He has provided research support for Lilly, Roche, and the National Institute on Aging. He has served on a Speaker's Bureau for Acadia, Biogen, and Eisai and has served on Safety Monitoring Committees for Anavex, EryDel, IntracellularTherapies, Merck, Newron, and Otlgonemx.
D Boggs, **C Streicher**, and **H Tabuteau** are current employees of Axsome Therapeutics, Inc.

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Methods

AXS-05 in MDD: Clinical Development Program

- The **ASCEND** Phase 2 and **GEMINI** Phase 3 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 MDD[5,6]
- The **COMET** study was an additional long-term, Phase 3, open label, multi-center, safety and efficacy study (N=876)

Key inclusion criteria across studies included:
- ✓ Male or female **18-65 years** of age
- ✓ DSM-5 criteria for current MDD without psychotic features
- ✓ Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≥25

ASCEND STUDY
Screening Period: Patients with a confirmed diagnosis of moderate or severe MDD
N = 80, 1:1 randomization
Double-blind Dosing Period (6 weeks): AXS-05 (n = 43); BUP (105 mg) (n = 37)
Primary endpoint: Change from baseline in ***MADRS*** total score over the 6-week treatment period, calculated at each time point and averaged (overall treatment effect)

GEMINI STUDY
Screening Period: Patients with a confirmed diagnosis of moderate or severe MDD
N = 327, 1:1 randomization
Double-blind Dosing Period (6 weeks): AXS-05 (n = 163); Placebo (n = 164)
Primary endpoint: Change from baseline in ***MADRS*** total score at Week 6
Key secondary endpoint: Change from baseline in ***MADRS*** total score at Week 1

Abbreviations: BID = twice-daily; BUP = bupropion; DM = dextromethorphan; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder

AXS-05 in AD Agitation: Clinical Development Program

- Four Phase 3 studies assessed efficacy and safety of AXS-05 for AD agitation

ADVANCE-1	ADVANCE-2	ACCORD-1	ACCORD-2
Randomized, double-blind, active & placebo-controlled.	*Randomized*, double-blind, placebo-controlled.	*Randomized withdrawal*, double-blind, placebo-controlled.	*Randomized withdrawal*, double-blind, placebo-controlled.
5 weeks	5 weeks	Up to 26 weeks	Up to 24 weeks
N = 366	N = 408	N = 108	N = 167
Primary endpoint: Mean reduction from baseline in the Cohen-Mansfield Agitation Inventory (***CMAI***) total score at Week 5	**Primary endpoint**: Mean reduction from baseline in the ***CMAI*** total score at Week 5†	**Primary endpoint**: Time from randomization to relapse of AD agitation	**Primary endpoint**: Time to relapse of AD agitation vs placebo

Key inclusion criteria across studies included:
- ✓ **65-95 years** of age
- ✓ Diagnosis of probable AD (NIA-AA) and clinically significant agitation resulting from probable AD

ADVANCE-1
Screening Period: Patients with probable diagnosis of AD and clinically significant agitation
N = 366, Randomization[a]
Double-blind Phase (5 weeks): AXS-05 (n = 159); Bupropion (105 mg BID) (n = 49); Placebo (n = 158)

ACCORD-2
Open-label period (at least 8 weeks)[b]: AXS-05
Double-blind period baseline: 1:1 R n=167
Double-blind Period[c] (Up to 24 weeks): AXS-05 (n = 83); Placebo (n = 84)

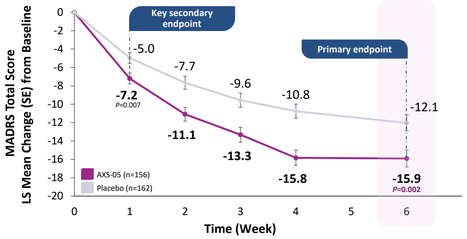
[a]ADVANCE-2 trial did not demonstrate statistical significance on primary endpoint; numerically greater improvements with AXS-05 over placebo (primary and secondary endpoints)
[a]An independent data monitoring committee performed an interim futility analysis and recommended no further randomization to the bupropion arm. Subsequently, patients were randomized in a 1:1 ratio to receive AXS-05 or placebo. [b]Eligible participants from the ADVANCE-2 were carried over to participate in ACCORD-2. [c]Participants who completed the double-blind treatment or had a relapse were eligible to return to open label treatment, if their total participation did not exceed 52 weeks.
Abbreviations: AD = Alzheimer's disease; BID = twice daily; BUP = bupropion; DM = dextromethorphan; NIA-AA = National Institute on Aging and Alzheimer's Association

Results

AXS-05 in MDD: Efficacy and Safety

- The **ASCEND** and **GEMINI** studies demonstrated rapid and sustained symptom improvement in MDD compared to placebo and bupropion, respectively[4,5]
- In the long-term **COMET** study, patients who received open-label AXS-05 demonstrated MADRS total score improvement over 12 months

GEMINI: Change from Baseline in MADRS Total Score over Time*

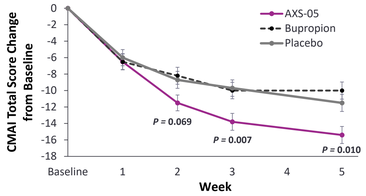


- The most commonly reported adverse reactions in **GEMINI** (≥5% and twice the rate of placebo) with AXS-05 were dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis[2]
- **GEMINI** and **ASCEND** had generally similar safety profiles, with no new signals detected in the long-term **COMET** study

* Modified intention to treat population: all patients who were randomized, received at least 1 dose of study medication, and had at least 1 post-baseline efficacy assessment. Missing data were not included; Endpoints analyzed using Mixed Model Repeated Measures (MMRM) Abbreviations: AE = adverse event; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; SE = standard error; TEAE = treatment emergent adverse event

AXS-05 in AD Agitation: Efficacy and Safety

ADVANCE-1: Change in CMAI total score



ADVANCE-1: Summary of Treatment-Emergent Adverse Events†

	AXS-05 (n = 159)	BUP (n = 49)	Placebo (n = 158)
Subjects with any TEAE	70 (44.0)	30 (61.2)	52 (32.9)
Somnolence	13 (8.2%)	2 (4.1%)	5 (3.2%)
Dizziness	10 (6.3%)	5 (10.2%)	5 (3.2%)
Diarrhea	7 (4.4%)	3 (6.1%)	7 (4.4%)
Headache	6 (3.8%)	3 (6.1%)	4 (2.5%)

- In **ADVANCE-1**, AXS-05 met the primary endpoint in demonstrating a statistically significant mean reduction in the CMAI total score compared to placebo at Week 5
- In the **ACCORD-1** and **ACCORD-2** studies, AXS-05 also met primary endpoints by delaying the time to relapse of AD agitation symptoms compared to placebo

- In **ADVANCE-1**, percent of participants with ≥ 1 TEAE (AXS-05, bupropion, and placebo, respectively) were 44%, 61.2%, and 32.9%, and with a serious TEAE were 3.1%, 8.2%, and 5.7%
- AXS-05 was generally well tolerated **across all studies**, further supporting the continued development of AXS-05 as a promising treatment option for AD agitation

*P-values are calculated from LS mean
†Safety Population. Data presented as number of subjects (% of subjects). Top four most prevalent TEAEs shown
Abbreviations: CMAI = Cohen-Mansfield Agitation Inventory; TEAE = treatment-emergent adverse event

Conclusions

- AXS-05 demonstrated rapid and clinically significant improvement in depressive symptoms across multiple studies in MDD, supporting the development and FDA-approval of dextromethorphan-bupropion for the treatment of MDD[2,4,5]
- AXS-05 significantly improved AD agitation symptoms (ADVANCE-1) and delayed time to agitation relapse (ACCORD-1 and -2) supporting the clinical development of AXS-05 for the treatment of AD agitation*
- AXS-05 was well tolerated in both populations
- Education on existing MDD treatments and potential upcoming treatments in AD agitation is crucial to inform patient care

* Dextromethorphan-bupropion (AXS-05) is not currently FDA-approved for use in AD agitation