Impact of AXS-05 (dextromethorphan-bupropion) on Depressive Symptoms, Anxiety, and Quality of Life in Patients with One Prior Treatment Failure: Results from the EVOLVE Long-Term, Open-Label Study

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Key Question

- How does long-term AXS-05 treatment impact depression symptoms, anxiety, and quality of life in people with depression treated with at least 1 prior treatment in their current MDE?

Conclusions

- Treatment with AXS-05 for up to 1 year rapidly and durably improved quality of life in people with MDD who failed 1 prior antidepressant in the current MDE
- Improvements occurred across the broad range of items associated with quality of life including overall life satisfaction, sense of well being, and ability to function in daily life
- In a naturalistic setting, treatment with AXS-05 also rapidly and durably improved depression and anxiety symptoms
- Long-term treatment with AXS-05 was generally well tolerated
- These data support the long-term efficacy and safety of AXS-05 in this patient population

References

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Disclosures

G Mattingly serves as a speaker for AbbVie, Alkermes, Axsome, Corium, Intracellular, Ironshore, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Sunovion, Supernus, Takeda, and Trispharma; a consultant for AbbVie, Alkermes, Axsome, Biogen, Corium, Eisai, Ironshore, Intracellular, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Redax, Roche, Sage, Sirona, Sunovion, Supernus, Takeda, and Teva; and a researcher for Abbvie, Alkermes, Akili, Axsome, Boehringer, Emalex, Idorsia, Janssen, Karuna, Lumos, Labs, Medgenics, Neurocrine, NLS-1 Pharma AG, Otsuka, Redax, Relmada, Roche, Sage, Sirtsi, Sunovion, Supernus, Takeda, and Teva.

A Jones is an employee of Transcend Therapeutics and was an employee of Axsome Therapeutics Inc. at the time of study conduct

S Alter, C Streicher, Z Thomas, and **H Tabuteau** are employees of Axsome Therapeutics Inc.

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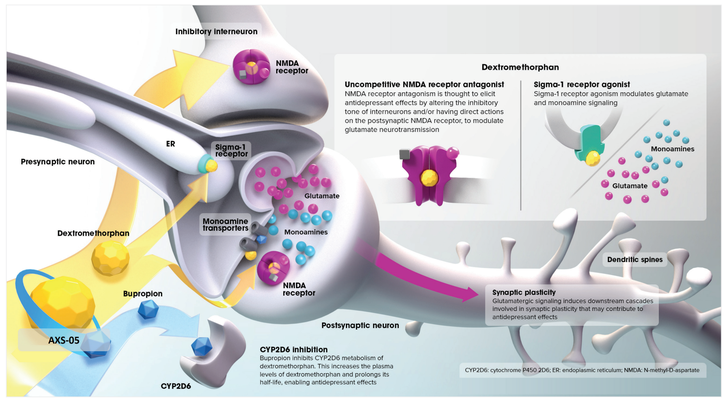
Introduction

- People with major depressive disorder (MDD) have significantly impaired quality of life, with lower quality of life than other chronic diseases[1]
- In the STAR*D trial, only 41% of patients responded to first-line SSRI treatment and remission rates decreased from 25.5% for first-line treatment to 10.4% by the fourth-line treatment[2]
- In people who respond to monoaminergic antidepressants, it often takes weeks to observe clinically meaningful improvements in depression and improvements in quality of life generally lag behind symptomatic improvements[2,3]
- Quality of life does not return to normal with antidepressant treatment for most people, even in those with remission of depression[1,3]
- Mechanistically novel, fast, and effective approaches to depression treatment which also improve quality of life are needed

AXS-05: A Novel, Oral NMDA Receptor Antagonist

- AXS-05 (dextromethorphan-bupropion [Auvelity® extended-release tablet]) is a novel, oral, N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist approved by the US Food and Drug Administration for the treatment of MDD in adults[4]
  - Dextromethorphan is an antagonist of the NMDA receptor and a sigma-1 receptor agonist[4]
  - Bupropion is an aminoketone and cytochrome P450 2D6 inhibitor that increases the bioavailability of dextromethorphan[4]

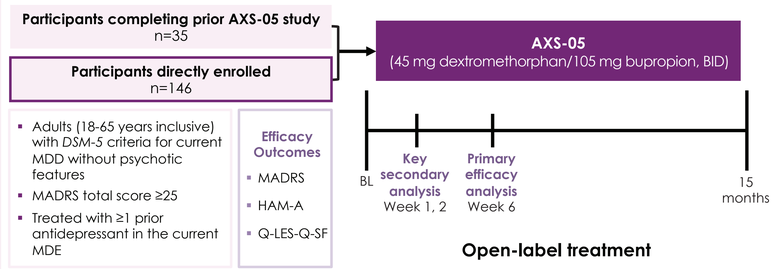
Figure 1. AXS-05 mechanism of action



Methods & Study Design

- EVOLVE (Evaluation of NMDA Modulation for Depressive Episodes, NCT04634669) was an open-label, phase 2, US trial, investigating AXS-05 in people with MDD treated with at least 1 prior treatment in their current MDE (**Figure 2**)
- This analysis presents efficacy endpoints in the *de novo* participants who were directly enrolled (n=146 safety population, n=145 modified intent-to-treat population), with an emphasis on quality of life as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF; **Figure 3**)

Figure 2. Study design



BID, twice daily; BL, baseline; *DSM-5, Diagnostic and statistical manual of mental disorders* 5th edition; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.

Figure 3. Q-LES-Q-SF individual items and scoring[5]

Q-LES-Q-SF Items		Scoring
Physical health	Ability to function in daily life	1 Very poor; 2 Poor; 3 Fair; 4 Good; 5 Very good
Mood	Sex drive, interest, performance	
Work	Economic status	
Household activities	Living/housing situation	
Social relationships	Ability to get around physically	
Family relationships	Vision in ability to do work/hobbies	
Leisure time activities	Overall sense of well being	
Medication	Overall life satisfaction	2 additional items not included in total score

Raw total score is the 14 items summed (14-70 total score) and then converted to **percent score** of maximum possible score

Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.

Key Findings

Patient Population

- At baseline, participants had moderate-to-severe depression, mild-to-moderate anxiety, and severely impaired quality of life (**Table 1**)

Depression and Anxiety Symptoms

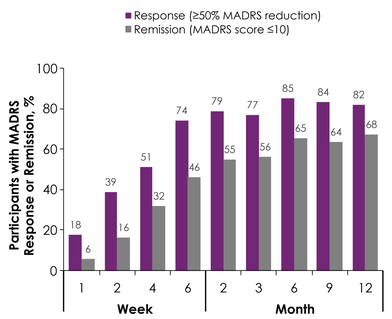
- AXS-05 treatment significantly improved depression symptoms as early as Week 1, with durable improvement for the 12-month open-label treatment period (**Figure 6**)
- Montgomery Åsberg Depression Rating Scale (MADRS) response and remission rates generally increased over the study (**Figure 4**)

Table 1. Baseline demographics and characteristics (mITT)

	AXS-05 (N=145)
Age, mean (SD), years	45.6 (13.07)
Sex, n (%)	
Women	88 (60.7)
Men	57 (39.3)
Race, n (%)	
White	112 (77.2)
Black	25 (17.2)
Asian	3 (2.1)
Other or multiple	5 (3.4)
MADRS total score, mean (SD)	32.2 (4.14)
CGI-S total score, mean (SD)	4.5 (0.55)
HAM-A, mean (SD)	15.6 (5.56)
Q-LES-Q-SF percent score, mean (SD)[a]	41.6 (12.00)

[a] Q-LES-Q scores ≥70.5% are within normal while scores ≤55.7% are severely impaired.[3]
CGI-S, Clinical Global Impressions Scale – Severity; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; mITT, modified intent-to-treat population; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.

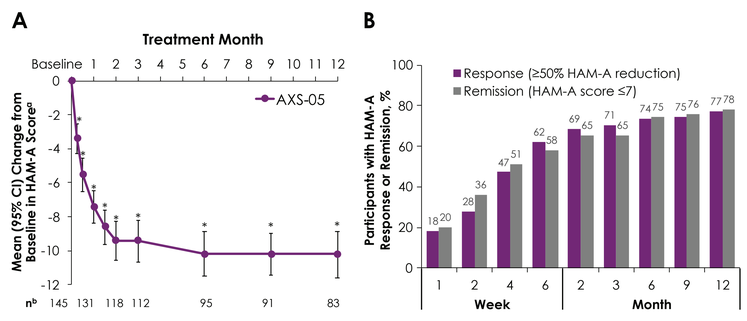
Figure 4. MADRS total score response and remission



MADRS, Montgomery Åsberg Depression Rating Scale.

- There were significant reductions from baseline in anxiety symptoms at every visit, which were durable through Month 12 (**Figure 5A**)
- Hamilton Anxiety Rating Scale (HAM-A) response and remission increased for the duration of the study (**Figure 5B**)

Figure 5. HAM-A score change from baseline (A) and response and remission (B)

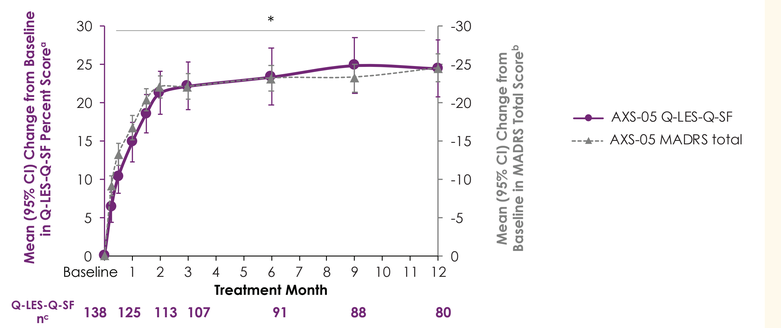


*P<.001 for change from baseline calculated by 2-sided paired t-test.
[a] Lower score indicates improvement. [b] Sample size at Week 1, n=141; Week 2, n=136; Week 6, n=124.
HAM-A, Hamilton Anxiety Rating Scale.

Quality of Life

- AXS-05 treatment also rapidly improved quality of life, with significant Q-LES-Q-SF percent score improvement from baseline at every visit, which mirrored improvements in depression symptoms (**Figure 6**)

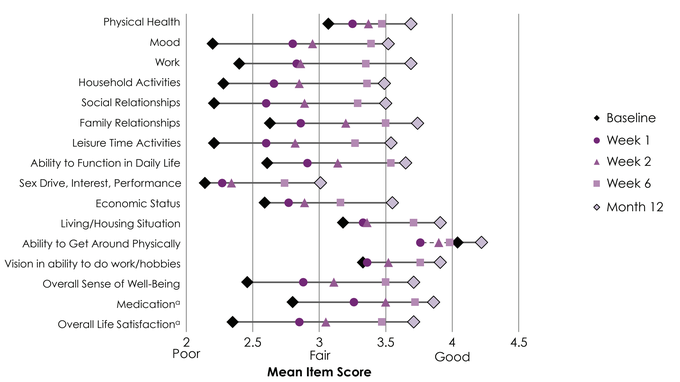
Figure 6. Q-LES-Q-SF percent and MADRS total score change from baseline



*P<.001 for change from baseline calculated by 2-sided paired t-test for all timepoints.
[a] Higher score indicates improvement. [b] Lower score indicates improvement. [c] Sample size at week 1, n=134; week 2, n=130; week 6, n=119.
MADRS, Montgomery Åsberg Depression Rating Scale; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.

- All individual Q-LES-Q-SF items had consistent improvements from baseline except *ability to get around physically*, which had the highest baseline score (4.04, good) (**Figure 7**)

Figure 7. Q-LES-Q-SF individual items



[a] Q-LES-Q-SF item not included in percent score.
Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.

Safety

- Long-term AXS-05 treatment was well tolerated
- Treatment-emergent adverse events (TEAEs) were experienced by 64.4% of participants and 41.1% experienced a drug-related TEAE
- There were no deaths during the study; 5 participants (3.4%) experienced serious TEAEs, and 13 participants (8.9%) discontinued due to a TEAE
- The most common (≥5%) TEAEs were COVID-19 infection (8.9%), nausea (8.9%), headache (7.5%), dry mouth (6.2%), insomnia (5.5%), and dizziness (5.5%)