AXS-05 Reduces Agitation in Alzheimer's Disease Patients

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> Agitation affects a substantial proportion of patients with Alzheimer's disease, leading to significant distress for both patients and caregivers, often precipitating institutionalisation. Current pharmacological options are limited, frequently carrying substantial side effect burdens that complicate long-term management. The ACCORD-2 trial aimed to evaluate a novel approach to this challenging symptom.

KEY TAKEAWAYS

- The Pivot: AXS-05 demonstrated a statistically significant reduction in agitation symptoms in Alzheimer's disease.
- The Data: The primary endpoint, change from baseline in CMAI total score, showed a mean difference of -4.5 points (pThe Action: Clinicians should consider AXS-05 as a potential treatment option for agitation in Alzheimer's disease, pending regulatory review.

Agitation represents one of the most pervasive and distressing neuropsychiatric symptoms associated with Alzheimer's disease, impacting up to 80% of patients over the course of their illness. This symptom complex, characterised by excessive motor activity, verbal aggression, and emotional lability, not only diminishes patient quality of life but also places immense strain on caregivers, often serving as a primary driver for nursing home placement. Existing treatments, primarily off-label antipsychotics, carry significant risks including increased mortality, cerebrovascular events, and accelerated cognitive decline, leaving a substantial unmet need for safer, more effective interventions.1
AXS-05, an oral, investigational medicine, combines dextromethorphan (DM) and bupropion (BUP) in a fixed-dose formulation. Dextromethorphan acts as an NMDA receptor antagonist and sigma-1 receptor agonist, while bupropion serves to increase the bioavailability of dextromethorphan by inhibiting CYP2D6, the primary enzyme responsible for DM metabolism. This dual mechanism targets glutamatergic overactivity and modulates serotonergic and noradrenergic pathways, which are implicated in the pathophysiology of agitation. The ACCORD-2 trial, a Phase III, open-label, safety extension study, evaluated the long-term safety and efficacy of AXS-05 in patients with Alzheimer's disease agitation.1

What the trial actually measured

The ACCORD-2 trial enrolled patients who had completed the preceding ADVANCE-1 or ADVANCE-2 studies, both placebo-controlled trials that established the short-term efficacy of AXS-05. Patients in ACCORD-2 received AXS-05 (45 mg dextromethorphan/105 mg bupropion) orally once daily for up to 52 weeks. The primary objectives focused on assessing the long-term safety and tolerability of AXS-05, with secondary objectives evaluating sustained efficacy using the Cohen-Mansfield Agitation Inventory (CMAI) total score, a 29-item scale widely used to quantify the frequency of agitated behaviors. Investigators also monitored cognitive function using the Mini-Mental State Examination (MMSE)

and overall clinical status with the Clinical Global Impression-Improvement (CGI-I) scale.1

Patients entering ACCORD-2 had a mean age of 74.5 years, with 58% being female. The baseline mean CMAI total score was 64.7, indicating moderate to severe agitation, and the mean MMSE score was 18.2, consistent with mild to moderate Alzheimer's dementia. The study population was diverse, reflecting a typical clinical cohort for Alzheimer's disease. Patients with significant psychiatric comorbidities or other neurological disorders were excluded, ensuring the observed effects were attributable to Alzheimer's-related agitation. The trial design allowed for dose adjustments in cases of intolerance, but the majority of patients maintained the target dose throughout the study period.1

AXS-05 maintained its efficacy over the 52-week extension period. Patients who continued AXS-05 treatment from the ADVANCE-2 trial showed a sustained reduction in CMAI total scores. The mean change from baseline in CMAI total score at Week 52 was -26.4 points (95% CI, -29.8 to -23.0). For patients who switched from placebo to AXS-05 in ACCORD-2, the mean reduction in CMAI total score was -24.3 points (95% CI, -27.5 to -21.1) after 52 weeks of AXS-05 treatment. These sustained reductions indicate that the initial benefits observed in the shorter-term trials did not wane with prolonged exposure.1

Safety data from ACCORD-2 reinforced the tolerability profile established in earlier studies. The most common adverse events (AEs) were falls (12.5%), urinary tract infection (10.3%), and headache (9.1%). Most AEs were mild to moderate in severity. Serious adverse events occurred in 18.7% of patients, with no single event type occurring in more than 2% of the cohort. Discontinuation due to AEs occurred in 10.8% of patients, a rate comparable to other treatments for neuropsychiatric symptoms in this vulnerable population. There were no new safety signals identified during the long-term extension, which is critical for a chronic condition like Alzheimer's disease.1

Cardiovascular safety, a concern with many psychotropic medications, was closely monitored. No significant changes in QTc interval were observed, and the incidence of cardiac adverse events was low and consistent with the patient population's age and comorbidities. Cognitive function, as measured by MMSE, remained stable or showed a slight improvement in some patients, suggesting AXS-05 did not exacerbate cognitive decline. This is a crucial distinction from antipsychotics, which often carry warnings about cognitive worsening. The open-label design is the obvious caveat for efficacy interpretation, as both patients and investigators were aware of the treatment assignment. This could introduce bias, particularly for subjective endpoints like agitation. However, the consistency of the observed effects across multiple trials and the sustained nature of the response lend credibility to the findings.1

The trial was not powered to detect differences in specific agitation subtypes, and that gap matters. Agitation is a heterogeneous syndrome, and understanding which specific behaviors respond best to AXS-05 could refine its clinical application. Furthermore, the study population was predominantly Caucasian, limiting the generalisability of the findings to more diverse ethnic groups. Whether benefits extend to patients with more severe dementia or those with significant cerebrovascular disease remains unclear, as these populations were largely excluded from the trial. Future research should address these limitations to fully characterise the utility of AXS-05 across the spectrum of Alzheimer's disease.1

> **CLINICAL IMPLICATIONS**
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> The sustained efficacy and safety profile of AXS-05 in the ACCORD-2 trial offer a welcome development for managing Alzheimer's disease agitation. For too long, clinicians have relied on off-label antipsychotics, knowing full well the increased risks of mortality and cognitive decline. This data provides a much-needed

alternative.

Axsome Therapeutics now has a stronger case for regulatory approval, potentially positioning AXS-05 as a first-line treatment. The absence of new safety signals over a year of treatment is particularly reassuring, given the chronic nature of Alzheimer's and the need for long-term symptom control.

But, the open-label nature of ACCORD-2 means some caution is warranted when interpreting the magnitude of effect. While the sustained reductions in CMAI scores are compelling, a truly blinded, long-term study would provide definitive evidence. Still, the consistent data across multiple trials suggests a genuine therapeutic effect.

The challenge now lies in integrating this new option into clinical practice. Education will be key for GPs and specialists to understand AXS-05's mechanism and differentiate it from older, less safe treatments. This drug could significantly improve the quality of life for patients and alleviate the burden on caregivers, if adopted appropriately.

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