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AXS-05 (Dextromethorphan/Bupropion): An Innovative Treatment in Clinical Development for Agitation Associated with Alzheimer's Disease

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Abstract

Background: Neuropsychiatric symptoms are prevalent in patients with Alzheimer's disease (AD) and cause great distress. Agitation, especially, is associated with early institutionalization, accelerated cognitive decline and increased mortality. Nevertheless, there are no FDA-approved treatments. AXS-05 is an innovative, oral, fixed-dose, combination of dextromethorphan and bupropion in clinical development for AD agitation. Dextromethorphan is an NMDA receptor antagonist, a sigma-1 receptor agonist and a serotonin and norepinephrine reuptake inhibitor. Extensive metabolism through CYP2D6 results in rapid elimination of dextromethorphan in humans. We have shown that bupropion, significantly inhibits the metabolism of dextromethorphan resulting in plasma concentrations associated with psychotherapeutic effects. AXS-05 therefore provides demonstrated pharmacokinetic and potential pharmacodynamic synergy between its active components. Agents that, like AXS-05, modulate glutamate signaling through NMDA and sigma-1 (e.g. memantine, fluvoxamine, donepezil) have shown effects in patients with behavioral disorders and AD. Dextromethorphan has previously been shown, in the presence of metabolic inhibition, to reduce agitation symptoms in AD, and the relevance of its serotonergic properties in this indication are further supported by clinical results with citalopram.

Methods: The pharmacokinetics of AXS-05, dextromethorphan, and bupropion, and the safety/tolerability of AXS-05, were assessed in Phase 1 trials. ADVANCE-1 is an ongoing Phase 2/3, randomized, double-blind, placebo and active-controlled (bupropion) 5-week study of AXS-05 in AD agitation. The primary efficacy outcome measure is the Cohen-Mansfield Agitation Inventory (CMAI). Interim analysis of ADVANCE-1 is planned.

Results: Significant increases in dextromethorphan plasma concentrations were observed with administration of AXS-05 in Phase 1 trials. AXS-05 was generally well-tolerated. The late-stage ADVANCE-1 study in AD agitation is ongoing and is expected to randomize approximately 435 subjects.

Conclusions: There is an urgent need for safe and effective treatments to tackle the clinical challenge of agitation in patients with AD. AXS-05 is a novel, oral, fixed-dose combination of dextromethorphan and bupropion. The potential of AXS-05 to ameliorate neuropsychiatric symptoms in AD is supported by the mechanisms of action of AXS-05, the positive pharmacokinetic interaction of its components, and clinical evidence with dextromethorphan and other agents which share the mechanisms of action of AXS-05. A Phase 2/3 clinical trial with AXS-05 in agitated patients with AD is ongoing.

Introduction

Alzheimer's disease agitation

Alzheimer's disease (AD) is an irreversible, progressive brain disorder that afflicts an estimated 5 million Americans, a number that is anticipated to increase to approximately 14 million by 2050. In addition to cognitive decline, individuals diagnosed with AD typically experience neuropsychiatric symptoms including agitation, aggression, depression, anxiety, apathy, delusions, and hallucinations. These neuropsychiatric symptoms are associated with decreased functioning, increased caregiver burden, earlier nursing home placement, accelerated progression to severe dementia, and increased risk of death. Specifically, agitation is associated with a significantly higher risk of institutionalization compared to most other neuropsychiatric symptoms suggesting that effective treatment could delay or prevent nursing home placement. There are currently no FDA-approved medications for the treatment of agitation associated with dementia of the Alzheimer's type.

AXS-05 mechanism of action

AXS-05 is a novel, oral, investigational medicine consisting of dextromethorphan (DM) and bupropion (BUP), in late-stage clinical development for AD agitation, treatment resistant depression (TRD), and nicotine dependence.

	Pharmacodynamic Synergy		
Mechanism of Action	DM	BUP	AXS-05 DM+BUP
NMDA Receptor Antagonist	✓		✓
Sigma-1R Agonist	✓		✓
Norepinephrine Reuptake Inhibitor	✓	✓	✓
Serotonin Reuptake Inhibitor	✓		✓
Dopamine Reuptake Inhibitor		✓	✓
Nicotinic Ach Receptor Antagonist	✓	✓	✓

DM = Dextromethorphan; BUP = Bupropion. ✓Present

AXS-05's mechanisms include multiple actions (shown above) upon various neurotransmitter systems implicated in the pathogenesis of neuropsychiatric symptoms of AD. Administration of DM in the presence of metabolic inhibition resulted in a significant reduction in symptoms of agitation in a controlled trial of patients with AD. Bupropion's antidepressant effects and other pharmacological actions may be relevant to certain neurobehavioral symptoms of AD such as depression. The BUP component of AXS-05 leads to significantly increased DM plasma levels.

Clinical Development of AXS-05

Pharmacokinetic synergy has been demonstrated between the two components of AXS-05 in three Phase 1 studies. In all studies, administration of AXS-05 resulted in a significant increase in DM exposure at all doses evaluated. Late-stage studies in agitation associated with AD (ADVANCE) and TRD (STRIDE-1) and are ongoing.

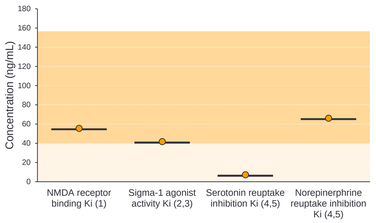
Agitation in AD: Clinical Rationale for AXS-05

Neurotransmitter System	AXS-05 Pharmacologic Effect	Clinical Evidence
Glutamate	NMDA Receptor Antagonism	• NMDA antagonism of AXS-05 is relevant based on clinical evidence suggesting altered glutamate transmission plays a role in behavioral and cognitive changes in dementia. • Pooled analysis suggests memantine (NMDA receptor antagonist) decreased the emergence of agitation, reduced agitation severity, and stabilized agitation symptoms compared to acetylcholinesterase inhibitors (AChEIs) alone.[1] • Co-administration of DM and a metabolic inhibitor (quinidine) has significantly reduced agitation symptoms in patients with AD.[2]
Sigma-1	Sigma-1 Receptor Agonism	• Clinical data with agents that, like AXS-05, target sigma-1 (e.g., fluvoxamine, donepezil) have shown efficacy in patients with behavioral disorders and Alzheimer's disease. • Positron emission tomography (PET) demonstrated a lower density of sigma-1 receptors in AD patients as compared to age-matched controls.[3]
Serotonin	Serotonin Reuptake Inhibition	• Positive clinical trial results with citalopram in AD patients with agitation favor a role for agents which, like AXS-05, target serotonin.[4]
Dopamine	Dopamine Reuptake Inhibition	• The bupropion component of AXS-05 robustly inhibits the metabolism of DM leading to DM plasma concentrations that are associated with a reduction in agitation symptoms in patients with AD (data on file). • Bupropion is a dopamine and norepinephrine reuptake inhibitor and a well-established antidepressant. Its known clinical activity and pharmacology may be relevant to other behavioral and psychological symptoms seen in AD patients such as depression and apathy.[5]

[1] Atri A, Agronin M, et al., *Neurology*. 2018;90(15):P6.175.
[2] Cummings J, et al. *JAMA*. 2015;314:1242-1254
[3] Mishina, et al., *Ann Nucl Med*. 2008;2(22):151-6.
[4] Porsteinsson AP, et al. *JAMA*. 2014;311(7):682-691.
[5] Corcoran C, Wong ML, O'Keane V. *J Psychopharmacol*. 2004;1(18):133-5; Marin RS, et al. *J Neuropsychiatry Clin Neurosci*. 1995;7(1):23-30; Steinberg H, et al. *Int J Geriatr Psychiatry*. 2008;2(23):170-7.

Overlap of AXS-05 DM Plasma Concentrations and DM K_i Values for Neurotransmitter Systems

DM neurotransmitter system K_i values compared to AXS-05 DM plasma concentrations

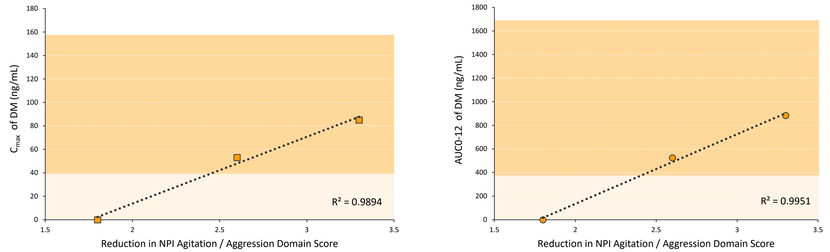


- Reported K_i values for DM at various neurotransmitter receptor systems are plotted and compared to DM plasma concentrations achieved with AXS-05 dosing in the Phase 1 pharmacokinetic trial.
- The shaded areas represent the DM plasma concentrations achieved with AXS-05. The horizontal lines represent the C_{max} achieved with the highest and lowest AXS-05 doses utilized in the Phase 1 trial.
- AXS-05 results in DM plasma concentrations that overlap with the reported K_i values for reuptake inhibition or binding by DM at these neurotransmitter receptor systems.

(1) Berman FW, et al. *J Biochem Toxicol*. 1996;11(5):217-226.
(2) Werling LL, et al. *Exp Neurol*. 2007;207(2):248-257.
(3) Robson MJ, et al. *Eur Neuropsychopharmacol*. 2012;22(4):308-317.
(4) Taylor CP, et al. *Pharmacol Ther*. 2016;164:170-182.
(5) Nishimura M, et al. *Anesthesiology*.1998;88(3):768-774.

DM Concentrations with AXS-05: Correlation with Agitation Symptom Reduction

Reduction in Symptoms of Agitation as a Function of DM Plasma levels



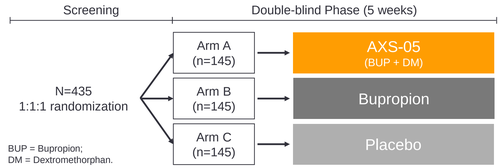
- Change in symptoms of agitation, reported in subjects with AD after co-administration of DM and the metabolic inhibitor quinidine, were plotted against the DM plasma concentrations associated with the doses used.
- AUC and C_{max} ranges achieved with AXS-05 in the Phase 1 trial are shown by the shaded area.
- The reduction in symptoms of AD agitation positively correlated with the DM plasma concentrations.
- AUC and C_{max} ranges for DM achieved with AXS-05 overlap with the DM levels associated with symptom reduction.

AD agitation symptom data from Cummings J, et al. *JAMA*. 2015;314:1242-1254. DM concentration data with DM/quinidine administration from NDA 021879, FDA Clinical Pharmacology Review. DM concentration data with AXS-05 administration from Axsome Therapeutics, Inc. (data on file).

Clinical Program with AXS-05 in Alzheimer's Disease Agitation

ADVANCE STUDY

A Phase 2/3 trial to assess the efficacy and safety of AXS-05 in the treatment of AD Agitation.



Primary Endpoint:
- Cohen-Mansfield Agitation Inventory (CMAI).

Key Inclusion Criteria:
- Diagnosis of probable Alzheimer's disease; Clinically significant agitation.

- 2nd Half of 2018: Interim analysis for futility is planned.
- 2019: Interim analysis for efficacy is planned.

www.advanceclinicalstudy.com
ClinicalTrials.gov Identifier: NCT03226522

Conclusion

- AXS-05 is a novel, oral, investigational medicine in clinical development for the treatment of agitation associated with AD.
- Clinical evidence with various agents that share the mechanisms of action of AXS-05 support its potential in the treatment of agitation in AD.
- AXS-05 results in increased DM plasma concentrations that overlap with the reported K_i values for reuptake inhibition or binding for neurotransmitter systems that are implicated in the pathology of agitation associated with AD.
- Reductions in symptoms of agitation in AD patients positively correlated with DM plasma concentrations.
- AXS-05 results in increased DM plasma concentrations that overlap with levels associated with reductions in symptoms of agitation in AD.
- An ongoing late-stage clinical trial is evaluating AXS-05 for agitation associated with AD. An interim analysis is planned for the second half of 2018.