# The Clinical Development and Therapeutic Potential of AXS-05 for Neuropsychiatric Disorders

Cedric O'Gorman, Amanda Jones, Kellie Kennon, Herriot Tabuteau

AXSOME THERAPEUTICS

25 Broadway, 9th Floor
New York, NY 10004 USA

For more information, please contact
Cedric O'Gorman at cogorman@axsome.com

## ABSTRACT

AXS-05, a novel, oral, fixed-dose combination of dextromethorphan and bupropion, is in late-stage clinical development for treatment-resistant depression and agitation associated with Alzheimer's disease. Dextromethorphan acts as an NMDA receptor antagonist, a sigma-1 receptor agonist and a reuptake inhibitor of both serotonin and norepinephrine. Dextromethorphan is extensively metabolized in humans. Plasma concentrations proposed for psychotherapeutic effects are only achieved in the presence of metabolic inhibition. Bupropion inhibits the breakdown of dextromethorphan in humans via CYP2D6. Bupropion is also an established antidepressant which acts as a dopamine and norepinephrine reuptake inhibitor. Both dextromethorphan and bupropion are nicotinic acetylcholine receptor antagonists. Clinical evidence with several classes of antidepressants, which individually share the mechanisms of action of AXS-05, support its development for treatment-resistant depression. Furthermore, the NMDA receptor antagonist property of AXS-05 may hold the potential for rapid onset of action based on the clinical experience with the prototypical NMDA receptor antagonist ketamine. Clinical evidence also suggests that glutamate transmission may play a role in the behavioral and cognitive changes in dementia. Clinical data with agents that, like AXS-05, target sigma-1 (e.g. fluvoxamine, donepezil) have shown effects in patients with behavioral disorders and Alzheimer's disease (AD). The role for the serotonergic properties of AXS-05 in AD patients with agitation is supported by clinical trial results with citalopram in this indication. Dextromethorphan has previously been reported, in the presence of metabolic inhibition, to reduce depressive symptoms in patients with TRD, AD and pseudobulbar affect, and to reduce agitation symptoms in patients with AD. Several Phase 1 trials assessed the pharmacokinetics of AXS-05, dextromethorphan and bupropion, as well as the safety and tolerability of AXS-05. A phase 3 randomized, double-blind active-controlled 12-week study is evaluating AXS-05 for the treatment of TRD. The primary efficacy outcome measure is the Montgomery-Åsberg Depression Rating Scale (MADRS). Additionally, a Phase 2/3, randomized, double-blind, placebo and active-controlled (bupropion) 5-week study is evaluating AXS-05 for the treatment of agitation associated with Alzheimer's disease. The primary efficacy outcome measure is the Cohen-Mansfield Agitation Inventory (CMAI). Administration of AXS-05 resulted in substantial increases in dextromethorphan plasma concentrations in Phase 1 trials. AXS-05 was safe and generally well tolerated. The STRIDE-1 study in patients with TRD is expected to enroll approximately 350 subjects. The ADVANCE-1 study in patients with AD is expected to enroll approximately 435 subjects. AXS-05 represents a novel innovative approach to the treatment of a number of neuropsychiatric disorders given the potential therapeutic synergy of the many clinically-relevant mechanisms of actions of dextromethorphan and bupropion.

## INTRODUCTION

**Scientific Rationale for AXS-05 (Bupropion/Dextromethorphan):** AXS-05 is a novel, oral, fixed-dose combination of dextromethorphan and bupropion in late-stage clinical development for treatment-resistant depression and agitation associated with Alzheimer's disease The rationale for combining bupropion and DM is based on the potential pharmacological synergy and the demonstrated pharmacokinetic synergy (from completed Phase 1 trials) between these two compounds. As bupropion and its metabolites are inhibitors of CYP2D6, co-administration of bupropion and DM leads to substantially increased DM plasma concentrations. Bupropion also contributes further centrally-acting mechanisms of action which have been found to be relevant for a variety of neuropsychiatric conditions. The centrally-acting mechanisms of action of bupropion in AXS-05 provide a potential for improved therapeutic effect.

**Treatment-Resistant Depression (TRD):** Results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial indicate that nearly two-thirds of treated patients with major depressive disorder (MDD) do not experience adequate treatment response with first-line therapy, and that the majority of these initial failures also fail second-line treatment. Unfortunately treatment options are limited for TRD. There is therefore an urgent need for effective and safe new treatments.

**Agitation Associated with Alzheimer's disease (AD):** Agitation and aggression are among the most burdensome and frequent neuropsychiatric symptoms afflicting patients with AD. These 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 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.

## MECHANISMS OF ACTION OF AXS-05

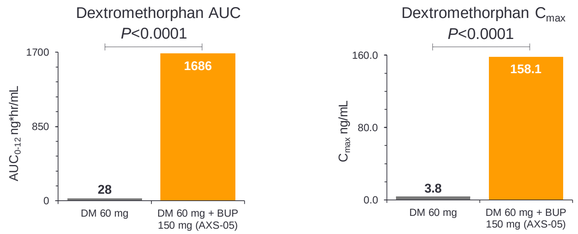
**Pharmacodynamic Synergy**

| 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

## PK SYNERGY ESTABLISHED IN 3 PHASE 1 STUDIES WITH AXS-05

**PHARMACOKINETIC SYNERGY: PHASE 1 RESULTS WITH AXS-05[1]**




[1]Axsome data on file.

**Objectives and Trial Designs:** 3 completed Phase 1 clinical trials of AXS-05 determined the pharmacokinetics of DM when co-administered with bupropion and assessed the safety and tolerability of the combination.

- **Study 101:** N=32; Randomized, multiple-dose, open-label study.
- **Study 102:** N=40; Randomized, multiple-dose, open-label study.
- **Study 103:** N=30; Randomized, multiple-dose, double-blind study.

**Results:** Substantial increases in DM plasma concentrations, measured using $C_{max}$ and AUC at all doses tested, were observed in all 3 studies when bupropion was administered in combination with DM. DM exposure increased in a dose-dependent manner as doses of either DM or bupropion were increased. Administration of DM did not affect the pharmacokinetics of bupropion.

The combination was safe and well tolerated. There was no difference in the rates or types of adverse events in the combination groups as compared to groups receiving bupropion alone. The majority of treatment-emergent adverse events were graded as mild or moderate in severity, and resolved by the end of the studies. No serious adverse events were reported.

## PRE-CLINICAL RATIONALE FOR AXS-05 IN TRD

Antidepressant-like effects of DM have been reported in two pre-clinical mice models: the forced swim test and the tail suspension test. Using the tail suspension test, DM resulted in effects similar to those seen with ketamine, a compound that has demonstrated fast-acting antidepressant effects. In both models, inhibition of DM metabolism using quinidine was shown to potentiate these antidepressant-like effects.

## CLINICAL RATIONALE FOR AXS-05

### Treatment Resistant Depression

- Clinical data with several marketed antidepressants, which share the mechanisms of action of AXS-05, support its development for TRD.
- AXS-05 possesses the mechanisms of action of 4 distinct antidepressant drug classes: 1) dopamine, norepinephrine reuptake inhibitor (eg bupropion), 2) SNRIs (eg venlafaxine), 3) sigma-1 receptor antagonists (eg fluvoxamine), and 4) NMDA receptor antagonists (eg ketamine).
- NMDA receptor antagonist property in AXS-05 may hold the potential for rapid onset of action based on the clinical experience with ketamine.
- The bupropion component of AXS-05 is a well-established antidepressant and robustly inhibits the metabolism of DM.
- Co-administration of DM and a metabolic inhibitor (quinidine) has reduced depressive symptoms in TRD, Alzheimer's disease[1,2] and pseudobulbar affect (PBA)[3].

### Agitation Associated with Alzheimer's Disease

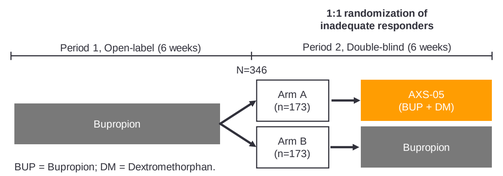
- The NMDA antagonism of AXS-05 is relevant based on clinical evidence suggesting that altered glutamate transmission plays a role in behavioral and cognitive changes in dementia.
- Clinical data with agents that, like AXS-05, target sigma-1 (eg fluvoxamine, donepezil) have shown efficacy in patients with behavioral disorders and Alzheimer's disease.
- Positive clinical trial results with citalopram in AD patients with agitation support a role for agents like AXS-05 which target serotonin[4].
- The bupropion component of AXS-05 robustly inhibits the metabolism of DM and may be relevant to other behavioral symptoms in AD.
- Co-administration of DM and a metabolic inhibitor (quinidine) has reduced agitation symptoms in patients with AD[2].

1.Murrough J. et al. *J Affect Disord.* 2017;218:277-283. 2. Cummings J. et al. *JAMA.* 2015;314:1242-1254.
3. Pioro EP. et al. *Ann Neurol.* 2010 Nov;68(5):693-702. 4. Porsteinsson AP. et al. *JAMA.* 2014;311(7):682-691.

## STUDY DESIGN OF LATE-STAGE CLINICAL PROGRAMS WITH AXS-05

Stride1Study AXS-05

**A Phase 3 trial to assess the efficacy and safety of AXS-05 for the treatment of TRD.**




**Primary Endpoint:**

- Change in depression score from randomization to end of study, measured using the Montgomery-Åsberg Depression Rating Scale (MADRS).

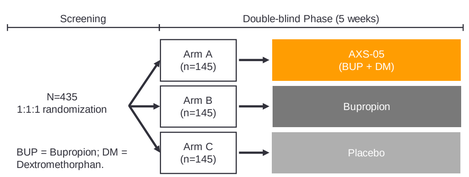
**Key Inclusion Criteria:**

- Male or female 18-65 years old; History of inadequate response to 1 or 2 adequate antidepressant treatments.

**www.trdstudy.com**
ClinicalTrials.gov Identifier: NCT02741791

ADVANCE STUDY

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




**Primary Endpoint:**

- Cohen-Mansfield Agitation Inventory (CMAI).

**Key Inclusion Criteria:**

- Diagnosis of probable Alzheimer's disease; Clinically significant agitation.

**www.advanceclinicalstudy.com**
ClinicalTrials.gov Identifier: NCT03226522

## CONCLUSION

AXS-05 is a novel, fixed-dose combination of dextromethorphan and bupropion. Dual potential pharmacodynamic and established pharmacokinetic synergy results in a unique pharmacological profile with potential efficacy in TRD and in agitation associated with AD. Ongoing late-stage clinical trials are evaluating AXS-05 for both indications. AXS-05 has received Fast Track designation from the FDA for both these indications.

**Disclosure:** COG, AJ, KK, and HT are employees of Axsome Therapeutics.