Clinical Development of AXS-05 for Treatment Resistant Depression and Agitation Associated with Alzheimer's Disease

Cedric O'Gorman[4], Dan V. Iosifescu[1,2], Amanda Jones[4], Kellie Kennon[4], Robert Niecestro[4], George I. Papakostas[3], Herriot Tabuteau[4]

[1]NYU School of Medicine, New York, NY; [2]Nathan Kline Institute, Orangeburg, NY; [3]Massachusetts General Hospital, Clinical Trials Network and Institute, Boston, MA; [4]Axsome Therapeutics, New York, NY.

AXSOME THERAPEUTICS

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

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

Abstract

OBJECTIVES: There are limited treatment options for patients suffering from treatment resistant depression (TRD) and agitation associated with Alzheimer's disease. An innovative, oral investigational agent, AXS-05, is in late-stage clinical development for both conditions. AXS-05 is a unique, fixed-dose combination of bupropion and dextromethorphan. Bupropion, a well-established antidepressant, serves to increase the bioavailability of dextromethorphan via inhibition of CYP2D6 leading to clinically relevant plasma levels. Pharmacologically, dextromethorphan is an NMDA-receptor antagonist, a sigma-1 receptor agonist and a reuptake inhibitor of both norepinephrine and serotonin. Bupropion is a norepinephrine and dopamine reuptake inhibitor and a nicotinic receptor antagonist. Strong preclinical and clinical data support the use of both bupropion and dextromethorphan for neuropsychiatric conditions. AXS-05 represents a potential therapeutic with both pharmacokinetic and pharmacodynamic synergies.

DESIGN: Three Phase 1 studies were completed to assess the pharmacokinetics of dextromethorphan after AXS-05 dosing in over 100 healthy volunteers. A variety of doses of dextromethorphan and bupropion were used in these studies. An ongoing Phase 3 randomized, double-blind, active-controlled, 12-week study (STRIDE-1) is evaluating the efficacy and safety of AXS-05 in subjects with TRD. This study consists of a 6-week open-label, bupropion lead-in period, and a 6-week double-blind treatment period. The Montgomery-Åsberg Depression Rating Scale (MADRS) total score is the primary efficacy outcome measure in this study. An ongoing Phase 2/3 randomized, double-blind, placebo-controlled 5-week study (ADVANCE-1) is evaluating the efficacy and safety of AXS-05 in subjects with agitation associated with Alzheimer's disease. The Cohen-Mansfield Agitation Inventory (CMAI) score is the primary endpoint in this study.

RESULTS: In the Phase 1 trials, which randomized over 100 subjects, co-administration of bupropion and dextromethorphan resulted in significantly higher plasma levels of dextromethorphan as measured by AUC and Cmax. No significant differences were observed in the rates or types of adverse events between groups administered AXS-05 and bupropion alone. The TRD study is expected to enroll approximately 350 subjects. The Alzheimer's agitation study is expected to enroll approximately 435 subjects.

CONCLUSION: TRD and agitation associated with Alzheimer's disease continue to lack appropriately safe and effective treatments. Along with a strong clinical and mechanistic rationale for the development of AXS-05 as a novel fixed-dose combination of dextromethorphan and bupropion for these conditions, our Phase 1 results demonstrate pharmacokinetic synergy with increased dextromethorphan bioavailability. Late-stage clinical programs with AXS-05 in TRD and agitation associated with Alzheimer's disease are ongoing.

Introduction

AXS-05 is a novel, oral, investigational medicine consisting of dextromethorphan (DM) and bupropion, in late-stage clinical development for TRD, Alzheimer's disease (AD) agitation 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 neurotransmitter actions (shown above), and anti-inflammatory actions. As bupropion (BUP) and its metabolites are inhibitors of CYP2D6, administration of AXS-05 leads to significantly increased DM plasma levels. 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. AXS-05 was safe and well tolerated. There was no difference in the rates or types of adverse events in the AXS-05 groups as compared to a group receiving BUP alone. No serious adverse events were reported in these studies. Late-stage studies in TRD (STRIDE-1) and agitation associated with AD (ADVANCE-1) are ongoing. In April 2018, an independent data monitoring committee (IDMC) performed a futility analysis on data from the first 40% of the target number of subjects from the STRIDE-1 study and recommended the study continue. The IDMC also indicated AXS-05 was safe and well-tolerated in the study.

Treatment-Resistant Depression (TRD): Approximately two-thirds of patients with MDD fail to achieve remission with first-line treatment according to results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Two-thirds of these patients also failed to remit on second-line treatment. TRD may be defined as having failed to respond to 2 or more adequate antidepressant treatments. There is an urgent need for a safe and effective treatment for this prevalent and disabling condition.

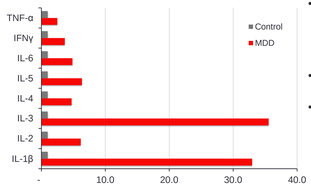
Agitation Associated with Alzheimer's disease (AD): There are about 50 million AD sufferers worldwide with that number expected to double over the next 20 years. More than half of AD sufferers experience symptoms of agitation and aggression. Of neuropsychiatric symptoms associated with dementia, agitation and aggression are amongst the most frequent and disruptive. The Cohen-Mansfield Agitation inventory (CMAI) groups symptoms into categories including verbal aggressive and non-aggressive, and physical aggressive and non-aggressive. Agitation in AD is associated with accelerated progression to severe dementia and earlier nursing home placement. There are no FDA-approved therapies for this condition.

Anti-Inflammatory Mechanisms of AXS-05

Anti-inflammatory Effects, and Antidepressant Effects in Inflammation-Induced Depression Models with AXS-05 Components

Cytokine	Changes in MDD	AXS-05 Pharmacologic Effect: Change	Component	Mechanistic Evidence
TNF-α	▲	▼	BUP, DM	• BUP prevented depressive-like behavior in mouse model of depression induced by TNF-α (Manosso 2013, Neis 2014). • BUP decreased serum elevations of TNF-α following intestinal ischemia-reperfusion (Cámara-Lemarroy 2013). • BUP lowers TNF-α in mouse LPS inflammation model (Brustolim 2006). • DM following TBI decreased TNF-α expression in rat (Pu 2015). • DM inhibited LPS-induced production of TNF-α in rats (Liu 2003).
Interferon-γ	▲	▼	BUP	• BUP lowers interferon-γ in mouse LPS inflammation model (Brustolim 2006).
IL-1β	▲	▼	BUP, DM	• BUP reduced edema, depressive-like behavior, and brain IL-1β levels in chronic inflammation-related depression model in mice (Maciel 2013). • BUP decreased serum elevations of IL-1 following intestinal ischemia-reperfusion (Cámara-Lemarroy 2013). • BUP lowers IL-1β in mouse LPS inflammation model (Brustolim 2006). • DM following TBI decreased IL-1β expression in rat (Pu 2015).
IL-6	▲	▼	DM	• DM following TBI decreased IL-6 expression in rat (Pu 2015).

Cytokine Levels in MDD Patients vs. Age and Gender Matched Healthy Controls



- Cytokine concentrations reported for MDD subjects were normalized to age and gender matched controls (resulting in value of 1 for controls).
- n=49 for MDD subjects, and n=49 for healthy controls.
- Raw data from Simon et al. 2008[1].

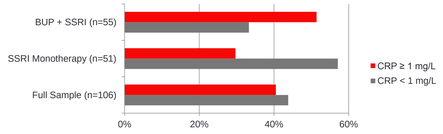
[1]Simon, N.M. et al. *Eur Neuropsychopharmacol*. 2008 Mar;18(3):230-3.

Overview

- Inflammation is implicated in both the pathophysiology of depression and in the lack of response to antidepressants.
- Increased levels of inflammatory markers have been reported in MDD patients as compared to age- and gender-matched healthy controls.
- In a recent study, approximately 70% of MMD patients had CRP levels ≥1 mg/L, indicative of systemic inflammatory activity.
- Both the BUP and DM components of AXS-05 have been shown to reduce the expression of inflammatory cytokines implicated in MDD.
- Clinical evidence with BUP plus SSRI treatment suggests that MDD patients with increased inflammatory markers may respond preferentially to AXS-05.

Response to Treatment with Bupropion Component of AXS-05 in Patients with Increased Inflammatory Markers

- MDD patients with higher baseline CRP levels (≥1 mg/L) had greater reductions in depression severity than those with lower CRP levels when treated with a combination of BUP and escitalopram (correlation coefficient = -0.63), but not with escitalopram alone (correlation coefficient = 0.43).[1]
- Higher baseline IL-17 level was associated with greater reduction in depression severity (effect size = 0.78, p = 0.008) with BUP and escitalopram, but not escitalopram alone.[2]
- AXS-05 combines the mechanisms of action of BUP, an SSRI, and a glutamatergic agent.



Remission Rate During Acute Phase of CO-MED

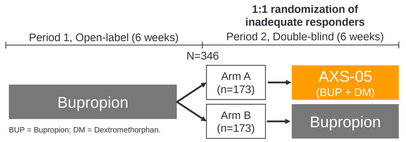
Remission of depression was assessed using QIDS-SR. Data courtesy of Manish K. Jha, MD, Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, United States.

[1]M.K. Jha, et al. *Psychoneuroendocrinology* 78 (2017) 105–113. [2]M.K. Jha, et al. *Brain Behav Immun*. 2017 Nov;66:103-110.

Status of Ongoing Clinical Programs with AXS-05 in TRD and Alzheimer's Disease Agitation

Stride1Study AXS-05

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



BUP = Bupropion; DM = Dextromethorphan.

Primary Endpoint:
Change in Montgomery-Åsberg Depression Rating Scale (MADRS) from randomization to end of study.

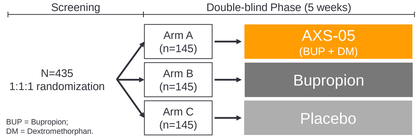
Key Inclusion Criteria:
Male or female 18-65 years old; History of inadequate response to 1 or 2 adequate antidepressant treatments.

- April 2018: An independent data monitoring committee (IDMC) recommended continuation of the STRIDE-1 study based on an interim analysis for futility. IDMC indicated that AXS-05 was safe and generally well tolerated.
- 2nd Half of 2018: Interim analysis for efficacy is planned.

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.



BUP = Bupropion;
DM = Dextromethorphan.

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

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

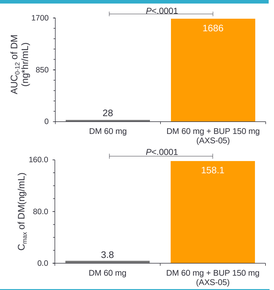
- 2nd Half of 2018: Interim analysis for futility is planned.
- 2019: Interim analysis for efficacy is planned.

www.advanceclinicalstudy.com
ClinicalTrials.gov Identifier: NCT03226522

DM Pharmacokinetics with AXS-05

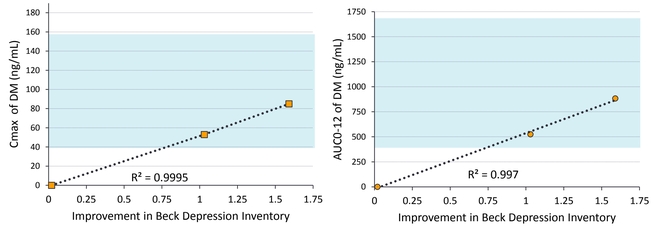
Phase 1 Pharmacokinetic Trial of AXS-05

- A total of 32 subjects were randomized to receive AXS-05 (BUP+DM) consisting of 150 mg of BUP and DM at various doses up to 60 mg, or 60 mg of DM alone, for 8 consecutive days, titrated to twice daily dosing. Full pharmacokinetic assessments were made on Day 1 and Day 8.
- For the AXS-05 dose of BUP 150 mg/DM 60 mg, $AUC_{0\text{-}12}$ and C_{max} values on Day 8 for DM after AXS-05 administration were approximately 60 times and 40 times, respectively, the values for DM when dosed alone. For all doses tested, administration of AXS-05 resulted in substantial increases in $AUC_{0\text{-}12}$ and C_{max} values of DM on Day 8 as compared to Day 1 of dosing. DM exposure measured using AUC and C_{max} increased in a dose dependent manner with increasing doses of AXS-05. DM did not appear to affect the pharmacokinetics of bupropion with AXS-05 dosing.
- AXS-05 was well tolerated with the most common AEs in patients treated with AXS-05 being headache, dizziness, and nausea. There were no SAEs in the trials.



Association of DM Concentrations with Symptom Reduction

Reduction in Depressive Symptoms as a Function of DM Plasma levels



- Change in depressive symptoms, reported in subjects with PBA 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 depressive symptoms 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.

Depressive symptom data from Pioro et al. *Ann Neurol*. 2010, vol. 68, no. 5, pp. 693-702. 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).

Conclusion

AXS-05 is a novel, oral, investigational medicine consisting of DM and BUP. AXS-05's mechanisms include monoaminergic, glutamatergic, and anti-inflammatory actions. Increased inflammatory markers have been reported in patients with MDD and TRD. AXS-05's anti-inflammatory mechanisms may contribute to its potential antidepressant effects. Improvements in depressive symptoms correlate positively with DM plasma concentrations. The positive pharmacokinetic interaction between the components of AXS-05 increase DM plasma concentrations into a range that overlap with levels associated with depressive symptom improvement. Ongoing late-stage clinical trials are evaluating AXS-05 for TRD and agitation associated with Alzheimer's disease.

Brustolim D et al. *Int Immunopharmacol*. 2006 Jun;6(6):903-7.
Cámara-Lemarroy CR et al. *Transplant Proc*. 2013 Jul-Aug;45(6):2502-5.
Liu Y et al. *J Pharmacol Exp Ther*. 2003 Apr;305(1):212-8.
Maciel IS et al. *PLoS One*. 2013 Sep 27;8(9):e77227.
Manosso LM et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013 Oct 1;46:48-57.
Neis VB et al. *Behav Brain Res*. 2014 Mar 15;261:336-44.
Pu B et al. *Mol Med Rep*. 2015 Sep;12(3):3704-10.

Disclosure:
COG, AJ, KK, RN and HT are employees of Axsome Therapeutics.
DVI is a consultant to Axsome Therapeutics.