AXS-05: A Mechanistically Novel Oral Therapeutic in Development for Neuropsychiatric Disorders

Cedric O'Gorman[2], Amanda Jones[2], James Davis[1], Herriot Tabuteau[2]

[1]Duke Center for Smoking Cessation, Duke University, Durham, NC; [2]Axsome Therapeutics, New York, NY.

AXSOME THERAPEUTICS

200 Broadway, 3rd Floor, New York, NY 10038 USA

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

Abstract

Introduction
AXS-05 is a novel, oral, investigational medicine that combines glutamatergic, monoaminergic, and anti-inflammatory mechanisms of action. AXS-05 consists of dextromethorphan (DM) and bupropion. The DM component is an N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist and an inhibitor of norepinephrine and serotonin reuptake. The bupropion component of AXS-05 serves to increase the bioavailability of DM and is a norepinephrine and dopamine reuptake inhibitor. Both components are nicotinic receptor antagonists and possess anti-inflammatory properties. These mechanisms of action may be relevant for various neuropsychiatric conditions. Pharmacokinetic data from completed Phase 1 trials of AXS-05 and clinical observations with the DM component indicate that AXS-05 increases DM concentrations into a potentially therapeutic range. AXS-05 is therefore being developed for the treatment of major depressive disorder (MDD), treatment resistant depression (TRD), agitation associated with Alzheimer's disease (AD), and nicotine dependence.

Methods
The efficacy and safety of AXS-05 are being evaluated in late-stage clinical trials. The potential of AXS-05 in the treatment of agitation associated with AD is being assessed in the ADVANCE Phase 2/3 trial, a randomized, double-blind, controlled trial in which subjects are randomized to treatment with AXS-05, placebo, or bupropion. The primary efficacy variable of the ADVANCE study is the Cohen Mansfield Agitation Inventory. The potential effects of AXS-05 in MDD are being evaluated in the ASCEND trial, a randomized, double-blind, active-controlled trial in which subjects are randomized to treatment with AXS-05 or bupropion. The primary efficacy variable of the ASCEND trial is the Montgomery Åsberg Depression Rating Scale. The potential effects of AXS-05 in TRD are being evaluated in the STRIDE-1 trial, which is a randomized, double-blind, active-controlled trial, with an open-label bupropion lead-in. Inadequate bupropion responders are randomized to treatment with AXS-05 or bupropion. AXS-05 is being evaluated as a therapeutic aid for smoking cessation in a randomized, active-controlled Phase 2 trial under a collaboration with the Duke Center for Smoking Cessation.

Results
Results of the ongoing efficacy trials with AXS-05 may be available at the time of the meeting. Potential results and/or status of the ongoing trials will be presented.

Conclusion
AXS-05 is an innovative, oral, investigational medicine with novel glutamatergic, monoaminergic, and anti-inflammatory mechanisms of action that may be relevant to the treatment of a variety of neuropsychiatric disorders including MDD, TRD, Alzheimer's disease agitation, and smoking cessation. The efficacy and safety of AXS-05 are being evaluated in a number of mid- and late-stage, randomized, controlled clinical trials. Latest data characterizing the potential effects of AXS-05 in the indications being evaluated will be presented.

Introduction

Major depressive disorder (MDD) is a leading cause of disability and a major contributor to disease burden worldwide. Results of the STAR*D trial indicate that as much as 70% of MDD patients experience an inadequate response to current first-line therapies, and that the majority of these patients also fail second line treatment.[1] In addition it can take 6-8 weeks to experience a clinically meaningful response for those who do respond.

Agitation is reported in up to 70% of patients with Alzheimer's disease (AD). Agitation is characterized by emotional distress, aggressive behaviors and disruptive irritability. Agitation in patients with AD has been associated with increased caregiver burden, decreased functioning, earlier nursing home placement, and increased mortality.[2,3] There are currently no therapies approved by the FDA for the treatment of agitation in patients with AD.

Smoking is the single largest cause of premature deaths worldwide accounting for an estimated almost 20% of all deaths in developed countries. It is estimated that only 3 to 5% of cigarette smokers who attempt to quit without assistance are successful for 6 to 12 months. Relapse rates remain above 80% even with current treatments.[4]

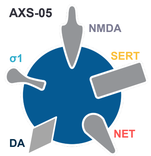
There is an urgent need for new and more effective medications to treat these conditions. The potential efficacy of AXS-05 in depression, AD agitation and smoking cessation is being evaluated.

[1]Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905-1917.
[2]Antonsdottir IM, et al. *Expert Opin Pharmacother.* 2015;11:1649-1656.
[3]Rabins PV et al. *Alzheimers Dement.* 2013; 9:204-207.
[4]Hughes JR, et al. *Addiction.* 2004;99:1, pp. 29-38.

AXS-05: Novel, Oral NMDA Antagonist with Multimodal Activity

AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, in clinical development for MDD, treatment resistant depression (TRD), AD agitation and smoking cessation. AXS-05 consists of dextromethorphan (DM) and bupropion, and utilizes Axsome's metabolic inhibition technology. The DM component of AXS-05 is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist, and an inhibitor of the serotonin and norepinephrine transporters. DM is rapidly and extensively metabolized in humans through CYP2D6 resulting in negligible plasma concentrations when given as a single agent. The bupropion component of AXS-05 serves to increase the bioavailability of DM, and is a norepinephrine and dopamine reuptake inhibitor. Both components are nicotinic acetylcholine receptor antagonists, and have demonstrated anti-inflammatory properties.

Neurotransmitter Targets of AXS-05



DA, dopamine; NET, norepinephrine transporter; NMDA, N-methyl-D-aspartate receptor; SERT, serotonin transporter; σ1, sigma-1 receptor.

	DM	Assay
NMDA receptor binding (IC_{50})	402 nM	•Rat cerebellar granule neurons[5]
Sigma-1 agonist activity (K_i)	150 nM	•Rat cerebellum[6] or PC12 cells[7]
Serotonin reuptake inhibition (K_i)	23 nM	•Rat brain synaptosomes[8] •Human kidney cells[9]
Norepinephrine reuptake inhibition (K_i)	240 nM	•Rat brain synaptosomes[8] •Human kidney cells[9]

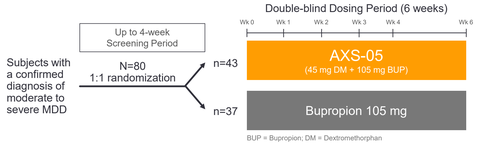
In completed Phase 1 pharmacokinetic trials, administration of AXS-05 resulted in DM plasma concentrations that overlap with the reported K_i values for reuptake inhibition or binding for DM at the above neurotransmitter receptor systems.

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

Results of Phase 2 ASCEND Trial of AXS-05 in Major Depressive Disorder

Methods
The ASCEND (Assessing Clinical Episodes in Depression) trial was a 6-week, randomized, double-blind, active-controlled multi-center trial. Eighty adult patients with a confirmed diagnosis of moderate to severe MDD were randomized in a 1:1 ratio to treatment with AXS-05 (n=43) or bupropion (n=37), twice daily for 6 weeks. The primary endpoint was the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, calculated at each study timepoint and averaged (overall treatment effect).

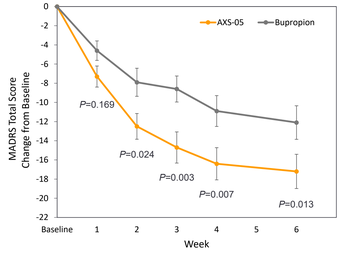
ASCEND (Assessing Clinical Episodes in Depression)



BUP = Bupropion; DM = Dextromethorphan

Results
- AXS-05 achieved the primary endpoint demonstrating a statistically significant mean reduction from baseline in the MADRS total score, calculated at each time point in the study and averaged, of 13.7 points for AXS-05 compared to 8.8 for bupropion (p<0.001).
- At Week 6, AXS-05 demonstrated a 17.2 point reduction in the MADRS total score compared to a 12.1 point reduction for bupropion (p=0.013).

Change in MADRS Total Score over Time



- AXS-05 rapidly reduced depressive symptoms, demonstrating a statistically significant improvement over bupropion on the CGI-I scale at Week 1 (p=0.045).
- Remission (MADRS total score of ≤ 10) was achieved by 47% of AXS-05 patients at Week 6, compared to 16% of bupropion patients (p=0.004).
- There were no serious adverse events (AEs) in the trial, and the most commonly reported AEs in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite, and anxiety. Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.

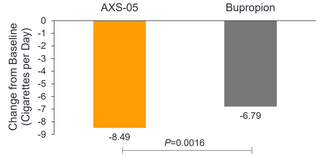
Conclusion
Administration AXS-05 was associated with a rapid and significant reduction in symptoms of depression as compared to the active comparator bupropion in patients with MDD. AXS-05 was safe and well-tolerated.

Results of Phase 2 Trial of AXS-05 in Smoking Cessation

Methods
A Phase 2, randomized, double-blind, active-controlled trial was conducted to evaluate the efficacy and safety of AXS-05 for smoking cessation treatment. A total of 58 smokers were randomized in a 1:1 ratio to receive either AXS-05 (45 mg dextromethorphan/105 mg bupropion) (n=31), or bupropion (105 mg) (n=27), twice daily, and assessed over a 3-week period. Enrolled subjects were daily smokers using at least 10 cigarettes per day. The average number of cigarettes smoked per day at baseline was 20 for AXS-05 and 17 for the bupropion treatment groups. The primary outcome measure was the change in smoking intensity measured using the number of cigarettes smoked per day, assessed via daily smoking diaries. The study was conducted at the Duke Center for Smoking Cessation.

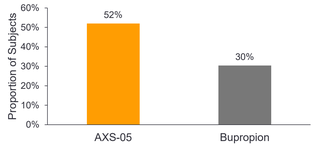
Results
- Treatment with AXS-05 resulted in a 25% greater reduction in the average number of cigarettes smoked per day over the 3-week period, the primary endpoint, as compared to bupropion (average reductions of 8.49 and 6.79 cigarettes per day for AXS-05 and bupropion, respectively, p=0.0016).
- Subjects who took AXS-05 as prescribed on a given day smoked 1.0 fewer cigarette on the day of medication use (p=0.026) and 1.2 fewer cigarettes on the following day (p=0.008) as compared to those who missed one or both doses. Subjects who took bupropion did not show an association between daily medication use and smoking.

Average Change in Cigarettes per Day over Three Weeks of Treatment with AXS-05 or Bupropion



- A greater proportion of smokers receiving AXS-05 experienced a more than 50% reduction in expired carbon monoxide levels, a biochemical marker of smoking intensity, as compared to those treated with bupropion (52.0% for AXS-05 versus 30.4% for bupropion, p=0.15).

Subjects Experiencing >50% Reduction in Expired Carbon Monoxide after Three Weeks of Treatment with AXS-05 or Bupropion

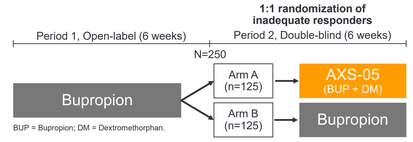


- Medication adherence was similar between the study arms for both the morning dose (97.1% for AXS-05 and 96.6% for bupropion) and the evening dose (76.3% for AXS-05 and 79.4% for bupropion).
- There were no serious AEs in the trial, and the most commonly reported AEs were headache, dry mouth, and insomnia/vivid dreams, with similar incidences in both treatment arms.

Conclusion
Administration of AXS-05 to smokers was associated with a significant reduction in smoking intensity, assessed by numbers of cigarettes smoked per day and exhaled carbon monoxide levels, as compared to the active comparator bupropion. AXS-05 was safe and well-tolerated.

Ongoing Clinical Programs with AXS-05

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



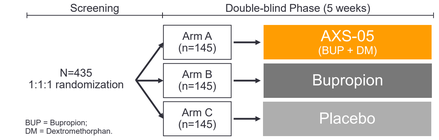
BUP = Bupropion; DM = Dextromethorphan.

Primary Endpoint
Montgomery-Åsberg Depression Rating Scale (MADRS) total score 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.

www.trdstudy.com
ClinicalTrials.gov Identifier: NCT02741791

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) Total Score.

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, oral NMDA antagonist with multimodal activity in late-stage clinical development for neuropsychiatric disorders. AXS-05 targets both glutamatergic (NMDA and sigma-1) and monoamine (serotonin, norepinephrine, dopamine) pathways, which have been shown to be relevant to the potential treatment of several CNS disorders.
- In a recently completed Phase 2 trial in patients with MDD, AXS-05 treatment was associated with a rapid and significant reduction in symptoms of depression as compared to the active comparator bupropion.
- In a recently completed Phase 2 trial in smoking cessation, AXS-05 treatment was associated with a significant reduction in cigarettes smoked per day, and a reduction in exhaled carbon monoxide levels, as compared to the active comparator bupropion.
- AXS-05 had been found to be safe and well tolerated.
- Late-stage clinical trials are ongoing to evaluate the efficacy and safety of AXS-05 in TRD and AD agitation.

Disclosures: COG, AJ and HT are employees of Axsome Therapeutics; JD is Director of the Duke Center for Smoking Cessation and Principal Investigator of the Phase 2 AXS-05 smoking cessation trial.