AXS-05 for Neuropsychiatric Disorders: Scientific Rationale and Clinical Development

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Abstract

Introduction: AXS-05 is a novel, oral, fixed-dose combination of dextromethorphan and bupropion currently in late-stage clinical development for treatment-resistant depression (TRD) and for 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. Due to extensive metabolism of dextromethorphan in humans, necessary plasma concentrations for proposed psychotherapeutic effects are not achievable in the absence of metabolic inhibition. Bupropion serves to inhibit 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 antidepressants in several pharmacological classes, which individually share the mechanisms of action of AXS-05, support its development for TRD. 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.

Methods: AXS-05 and it components have been evaluated in several Phase 1 pharmacokinetic trials involving over 100 patients. These studies examined the pharmacokinetics of dextromethorphan after AXS-05 dosing and assessed the safety and tolerability of AXS-05. STRIDE-1 is a Phase 3, randomized, double-blind, active-controlled, 12-week trial of AXS-05 in subjects with TRD. This study consists of a 6-week open-label, bupropion lead-in period, and a 6-week, randomized, double-blind treatment period with AXS-05 or bupropion. The primary efficacy outcome measure is the Montgomery-Åsberg Depression Rating Scale (MADRS). ADVANCE-1 is a Phase 2/3, randomized, double-blind, placebo-controlled, 5-week trial of AXS-05 in subjects experiencing agitation associated with AD. The primary efficacy outcome measure is the Cohen-Mansfield Agitation Inventory (CMAI).

Results: 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. Both STRIDE-1 and ADVANCE-1 incorporate interim analyses.

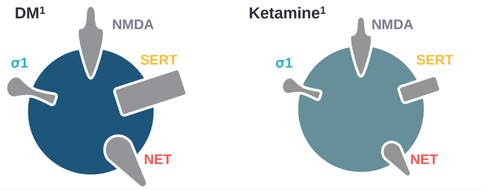
Conclusions: AXS-05 is an innovative, oral, fixed-dose combination of dextromethorphan and bupropion. Increased dextromethorphan bioavailability has been demonstrated with AXS-05 administration. The mechanisms of action of both dextromethorphan and bupropion, and several lines of clinical evidence with agents that share these mechanisms, support the development of AXS-05 for neuropsychiatric symptoms. Ongoing late-stage clinical trials are evaluating the efficacy and safety of AXS-05 in patients with TRD and in patients with agitation associated with AD.

Introduction

AXS-05 is a novel, oral, investigational medicine consisting of dextromethorphan (DM) and bupropion, in late-stage clinical development for TRD and agitation associated with Alzheimer's disease (AD). DM is an NMDA receptor antagonist, sigma-1 receptor agonist, and an inhibitor of the serotonin and norepinephrine transporters. Bupropion serves to increase the bioavailability of DM, and is a norepinephrine and dopamine reuptake inhibitor. Both DM and bupropion are also nicotinic acetylcholine receptor antagonists, and have anti-inflammatory properties. The biological pathways targeted by these pharmacological actions have been implicated in depressive disorders and in the neuropsychiatric symptoms of AD.

Ketamine treatment has been reported to result in rapid and substantial antidepressant efficacy in depressed patients. Limitations of ketamine include the need for parenteral administration, the potential for abuse and diversion, psychotomimetic effects, and a narrow therapeutic window. Similarities between the DM component of AXS-05 and ketamine, in terms of receptor pharmacology and pharmacodynamic effects, suggest the potential for antidepressant efficacy with AXS-05, without the limitations of ketamine.

Overlap in Activity of DM Component of AXS-05 and Ketamine on Neurotransmitter Targets

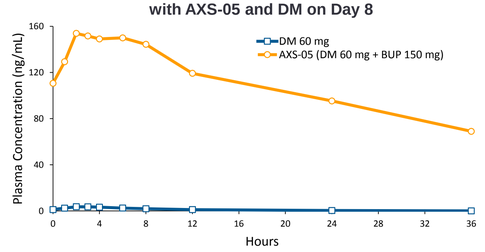


	DM	Ketamine	Assay
NMDA receptor binding (IC_{50})	402 nM	1047 nM	• Rat cerebellar granule neurons[2]
Sigma-1 agonist activity (K_i)	150 nM	140 μM	• Rat cerebellum[3] or PC12 cells[4]
Serotonin reuptake inhibition (K_i)	23 nM	162 μM	• Rat brain synaptosomes[5] • Human kidney cells[6]
Norepinephrine reuptake inhibition (K_i)	240 nM	67 μM	• Rat brain synaptosomes[5] • Human kidney cells[6]

[1]Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[2]Berman FW, et al. *J Biochem Toxicol*. 1996;11(5):217-226.
[3]Werling LL, et al. *Exp Neurol*. 2007;207(2):248-257.
[4]Robson MJ, et al. *Eur Neuropsychopharmacol*. 2012;22(4):308-317.
[5]Taylor CP, et al. *Pharmacol Ther*. 2016;164:170-182.
[6]Nishimura M, et al. *Anesthesiology*.1998;88(3):768-774.

DM Pharmacokinetics with AXS-05

DM Plasma Concentrations over Time with AXS-05 and DM on Day 8



DM Pharmacokinetic Parameters on Day 8

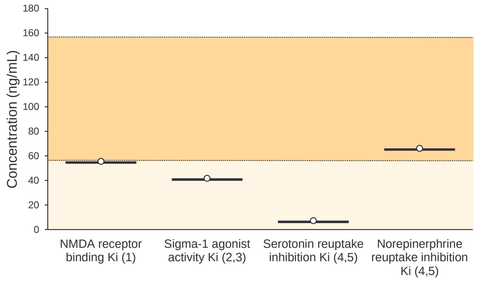
Treatment	AUC_{0-12} (ng/mL/hr)	AUC_{0-24} (ng/mL/hr)	AUC_{0-inf} (ng/mL/hr)	C_{max} (ng/mL)	$T_{1/2}$ (hr)
AXS-05 (DM 60mg + 150mg BUP)	1686 ± 692	2975 ± 1237	7237 ± 4557	158 ± 65	27.7 ± 11.5
DM (60mg)	28 ± 15	37 ± 20	41 ± 23	3.8 ± 1.9	6.6 ± 1.7

Phase 1 Results

- 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.
- DM plasma concentrations and elimination half-life were significantly increased with AXS-05 as compared to DM alone. Concentration time profiles and PK parameters for DM on Day 8 after dosing with AXS-05 (BUP 150 mg + DM 60 mg dose) and DM 60 mg are shown.
- For all doses tested, administration of AXS-05 resulted in substantial increases in AUC and C_{max} for DM on Day 8 as compared to Day 1. DM exposure increased with increasing doses of AXS-05. DM did not appear to affect the pharmacokinetics of bupropion with AXS-05 dosing.
- AXS-05 was safe and well tolerated with the most common AEs being headache, dizziness, and nausea. There were no SAEs in the trial.

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.
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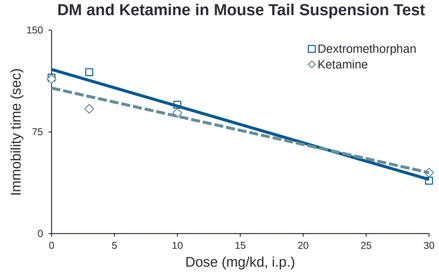
Antidepressant-like Effects of DM Component of AXS-05 and Ketamine in Mouse Tail Suspension Test

- The effects of DM and ketamine in the mouse tail suspension test (TST), a well-established model predictive of antidepressant efficacy, were plotted at various doses.
- DM reduced immobility time with comparable efficacy to ketamine in the TST in a dose-dependent manner (P<0.001 for 30 mg/kg versus 0 mg/kg, for both agents). Similar findings for DM and ketamine were also reported in the forced swim test (FST).[2]
- Ketamine increased locomotor activity whereas DM did not in the mouse, suggesting that DM can elicit antidepressant-like effects with a potentially more favorable side effect profile than ketamine.[2]
- Raw data for plot derived from Nguyen, et al. 2015.[1]

Comparison of Antidepressant-like Effects of DM and Ketamine in Mouse Tail Suspension Test

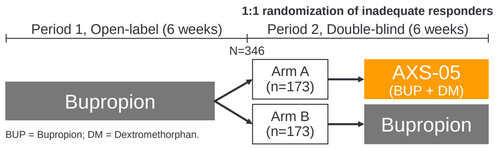


[1]Nguyen, et al. *Behav Brain Res*. 2015 Dec 15;295:26-34.
[2]Nguyen, et al. *Neuroreport*. 2016 Sept 28;27(14):1004–1011.

Status of Ongoing Clinical Programs with AXS-05 in TRD and AD Agitation

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

www.trdstudy.com
ClinicalTrials.gov Identifier: NCT02741791



BUP = Bupropion; DM = Dextromethorphan.

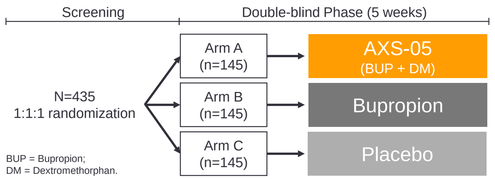
Primary Endpoint: Change in Montgomery-Åsberg Depression Rating Scale (MADRS) from randomization to end of study.

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.

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

www.advanceclinicalstudy.com
ClinicalTrials.gov Identifier: NCT03226522



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.

Conclusion

AXS-05 is a novel, oral, investigational medicine consisting of DM and bupropion. Analysis of reported K_i values for receptor binding and activity for NMDA, sigma-1, serotonin and norepinephrine indicate similar *in vitro* potencies for the DM component of AXS-05 and ketamine. The DM component of AXS-05 and ketamine exhibited similar antidepressant-like effects in the mouse TST and FST, while DM, unlike ketamine, did not increase locomotor activity, further supporting the potential for antidepressant efficacy with AXS-05, without the limitations of ketamine. AXS-05 dosing in a Phase 1 trial resulted in substantial increases in DM plasma concentrations and elimination half-life as compared to single-agent DM, enabling the use of DM for neuropsychiatric disorders. DM plasma concentrations with AXS-05 overlap with the reported K_i values of DM for receptor binding and activity for NMDA, sigma-1, serotonin and norepinephrine, supporting the potential for AXS-05 in the treatment of neuropsychiatric disorders. Late-stage clinical trials evaluating AXS-05 for TRD and agitation associated with AD, and a Phase 2 trial of AXS-05 in nicotine dependence, are ongoing.

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