AXS-05 for Neuropsychiatric Disorders: Scientific rationale and clinical development

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AXS-05 is a novel, oral, broad-spectrum combination of dextromethorphan and bupropion in late-stage clinical development for the treatment of 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 serotonin and norepinephrine. Due to extensive metabolism of dextromethorphan, clinical concentrations of the parent compounds for proposed psychotherapeutic effects are not detectable. Bupropion serves to inhibit the breakdown of dextromethorphan in humans via CYP2B6. Bupropion is also an adrenergic antidepressant which acts as a dopamine and norepinephrine reuptake inhibitor and as a nicotinic acetylcholine receptor antagonist.

Clinical evidence with antidepressants and other pharmacological classes, which individually share the mechanisms of action of AXS-05, supports 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 prototypic NMDA receptor antagonist ketamine. Clinical evidence also suggests that glutamate transmission may play a role in the behavioral and cognitive changes in Alzheimer’s disease.

Methods: AXS-05 and its components have been evaluated in several Phase 1 pharmacokinetic trials involving over 100 subjects. 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 2, 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 phase in part followed by a 6-week, randomized, double-blind treatment period with AXS-05 or placebo. The primary efficacy outcome measure is the Montgomery-Asberg Depression Rating Scale (MADRS).

Phase 1 Results

- AXS-05 was safe and generally well tolerated.
- AXS-05 exhibits a rapid onset of action based on the clinical experience with TRD.
- AXS-05 demonstrates substantial increases in AUC and Cmax when compared to AXS-05 alone, for 8 consecutive days, titrated to twice daily dosing.
- AXS-05 treatment was not associated with the limitations of single-agent antidepressants.

Conclusion

AXS-05 is a novel, oral, investigational medicine consisting of dextromethorphan (DM) and bupropion, in late-stage clinical development for the treatment of TRD and for agitation associated with Alzheimer’s disease. AXS-05 is an NMDA receptor antagonist, sigma-1 receptor agonist, and an inhibitor of the serotonin and norepinephrine reuptake 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.

Animal treatment has been reported to result in rapid and substantial antidepressant efficacy in depressed patients. Limitations of this animal model include the use of the most potent and sustained anticonvulsant strategy for depression, and 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 of AXS-05, without the limitations of the ketamine model.

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