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

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Abstract

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

AXS-05 is a novel, oral, investigational medicine that targets multiple neurotransmitter receptor systems and is in development for the treatment of agitation associated with Alzheimer's disease (AD) and major depressive disorder (MDD), as well as smoking cessation. AXS-05 is a fixed-dose combination of dextromethorphan (DM) and bupropion. DM is a potent and selective antagonist of N-methyl-D-aspartate (NMDA) receptor with rapid and extremely potent NMDA receptor antagonism in vivo, while bupropion is a norepinephrine and dopamine reuptake inhibitor that increases the bioavailability of DM, and is a norepinephrine and dopamine reuptake inhibitor. AXS-05 is in development for smoking cessation and has been shown to be safe and tolerable when administered as a smoking cessation aid in combination with nicotine replacement therapy. AXS-05 is also in development for the treatment of agitation associated with AD and major depressive disorder.

Methods

AXS-05: Assessing Clinical Episodes in Depression (Tread) 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 (45 mg DM + 105 mg bupropion) or bupropion (150 mg). The primary outcomes were remission and response using the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, calculated each time point in the study and averaged, of 13.7 points for MDD compared to 8.8 for bupropion (p=0.001). At Week 6, AXS-05 demonstrated a 1.7 point reduction in the MADRS total score compared to 0.17 point for bupropion (p=0.006).

Results

AXS-05 rapidly reduced depressive symptoms, demonstrating a statistically significant improvement compared to bupropion at all time points starting at Week 2 up to and including Week 6 (p<0.01). AXS-05’s MADRS total score of 12 was achieved by 41% of patients randomized to AXS-05 versus 28% of patients randomized to bupropion (p=0.008).

Conclusion

AXS-05 was efficacious in the treatment of moderate to severe MDD, resulting in a more rapid reduction in depressive symptoms compared to bupropion. AXS-05 was well-tolerated and considered safe for the treatment of moderate to severe MDD. AXS-05 has the potential to improve smoking cessation outcomes and the treatment of agitation associated with AD and MDD.

Ongoing Clinical Programs with AXS-05

AXS-05 is investigational. AXS-05 is not approved for, and has not been studied in, the treatment of smoking cessation. AXS-05 is not approved for, and has not been studied in, the treatment of agitation associated with AD. AXS-05 is not approved for, and has not been studied in, the treatment of major depressive disorder. AXS-05 is not approved for, and has not been studied in, the treatment of nicotine dependence. AXS-05 is not approved or studied in any indication in China.

Conclusion

AXS-05 is a novel, oral, investigational medicine that targets multiple neurotransmitter receptor systems and is in development for the treatment of agitation associated with AD and major depressive disorder, as well as smoking cessation. AXS-05 is in development for smoking cessation and has been shown to be safe and tolerable when administered as a smoking cessation aid in combination with nicotine replacement therapy. AXS-05 is also in development for the treatment of agitation associated with AD and major depressive disorder.