Safety and efficacy of KarXT (Xanomeline Tropium) in Schizophrenia in the Phase 3, Randomized, Double-Blind, Placebo-Controlled EMERGENT-2 Trial

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Abstract

Introduction. KarXT combines the M1/M4 preferring muscarinic receptor agonist xanomeline and the peripherally restricted anticholinergic trospium. In the phase 2 EMERGENT-1 study, KarXT met the primary endpoint of a significant reduction in Positive and Negative Syndrome Scale (PANSS) total score through week 5 vs placebo, improved other key secondary efficacy measures, and was generally well tolerated.

Methods. EMERGENT-2 was a phase 3, randomized, double-blind, placebo-controlled, 5-week trial of KarXT in acutely psychotic patients with schizophrenia in the inpatient setting. Eligible patients were randomized 1:1 to KarXT or matched placebo. Dosing of KarXT (mg xanomeline/mg trospium) started at 50 mg/20 mg BID and increased to a maximum of 125 mg/30 mg BID. The primary efficacy endpoint was change from baseline to week 5 in PANSS total score. Key secondary endpoints included change from baseline to week 5 in PANSS positive subscale, PANSS negative subscale, and PANSS negative Marder factor scores compared with placebo. Efficacy analyses were performed using the modified intent-to-treat population (patients with ≥1 dose of study medication, a baseline PANSS assessment, and ≥1 postbaseline PANSS assessment). All patients receiving ≥1 dose of study drug were included in safety analyses.

Results. 252 US patients were enrolled. KarXT demonstrated a statistically significant and clinically meaningful 9.6-point reduction from baseline to week 5 (effect size = 0.61) in PANSS total score vs placebo (p < 0.0001); a significant improvement in PANSS total score was demonstrated starting at week 2 (first postbaseline rating) and continued through the study end. KarXT also met key secondary endpoints. Results at week 5 included a 2.9-point reduction in PANSS positive subscale score with KarXT vs placebo (p < 0.0001), a 1.8-point reduction in PANSS negative subscale score with KarXT vs placebo (p = 0.0055), and a 2.2-point reduction in PANSS negative Marder factor score with KarXT vs placebo (p = 0.0022). KarXT was generally well tolerated. Overall discontinuation rates were similar with KarXT (25%) and placebo (21%). The overall treatment-emergent adverse events (TEAEs) rate for KarXT and placebo was 75% and 58%, respectively. Discontinuation rates related to TEAEs were similar between KarXT (7%) and placebo (6%). Rates of serious TEAEs were similar with KarXT and placebo (2%, each group); no serious TEAEs were determined to be drug related. The most common TEAEs (≥5%) with KarXT were all mild to moderate in severity and included constipation, dyspepsia, nausea, vomiting, headache, blood pressure increases, dizziness, gastroesophageal reflux disease, abdominal discomfort, and diarrhea. KarXT was not associated with sedation/somnia, weight gain, and extrapyramidal symptoms.

Conclusions. KarXT has the potential to be the first in a new class of treatments for patients with schizophrenia and a promising alternative to postsynaptic dopamine D2 receptor antagonists.

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