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ACNP TU270

Efficacy of Xanomeline and Trospium Chloride Across Symptom Domains in Adults With Schizophrenia: Results From the 52-Week, Open-Label EMERGENT-5 Clinical Trial

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*At the time the analysis was conducted

Background

- KarXT (xanomeline and trospium chloride) combines the dual M_1/M_4 preferring muscarinic receptor agonist xanomeline with the peripherally restricted pan muscarinic receptor antagonist trospium chloride.[1] KarXT was approved by the U.S. Food and Drug Administration for the treatment of schizophrenia in adults in 2024[2]
- KarXT was generally well tolerated and associated with significant symptom improvement in adults with schizophrenia experiencing acute psychosis in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials and in the 52-week, open-label EMERGENT-4 (NCT04659174) trial[1,3-6]
- Here, long-term KarXT efficacy is further explored in the 52-week, open-label EMERGENT-5 (NCT04820309) trial of adults who have a confirmed diagnosis of schizophrenia, stable symptoms, and no prior exposure to KarXT.[7] Post hoc analysis examined symptom improvement as assessed using Positive and Negative Syndrome Scale (PANSS) Marder 5-factor analysis, which classifies PANSS items into 5 dimensions to highlight distinct underlying processes in schizophrenia[8]

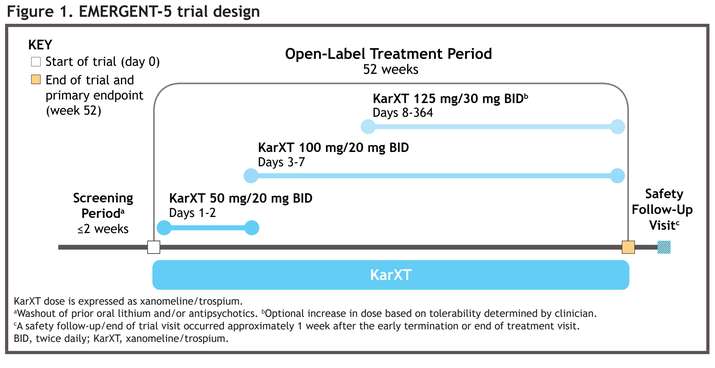
Objective

- To assess the long-term efficacy of KarXT in adults with schizophrenia who have stable symptoms, evaluated using PANSS Marder 5-factor analysis of data from the EMERGENT-5 clinical trial

Methods

- EMERGENT-5 was a phase 3, multicenter, 52-week, outpatient, open-label trial evaluating long-term safety, tolerability, and efficacy of KarXT in adults with schizophrenia (**Figure 1**)
- EMERGENT-5 enrolled psychiatrically stable participants aged 18-65 years with a primary diagnosis of schizophrenia, a PANSS total score ≤80, a Clinical Global Impression-Severity (CGI-S) score ≤4, and no prior exposure to KarXT
- After washout of prior antipsychotic medications, all participants initiated twice daily (BID) doses of KarXT at 50 mg/20 mg (xanomeline/trospium) and were titrated to a maximum dose of 125 mg/30 mg BID based on tolerability and investigator discretion for 52 weeks
- The primary endpoint was incidence of treatment-emergent adverse events (TEAEs)
  - TEAEs were assessed in the safety population, defined as all participants who received ≥1 dose of trial medication
- Prespecified efficacy assessments included change from baseline to week 52 in PANSS total, PANSS positive and negative subscale, and PANSS Marder negative factor scores; a post hoc analysis examined PANSS Marder positive, uncontrolled hostility, disorganized thought, and depression/anxiety factor scores
  - Efficacy analyses were performed in the modified intention-to-treat (mITT) population, defined as all participants who received ≥1 dose of KarXT and had a baseline and ≥1 postbaseline PANSS assessment

Figure 1. EMERGENT-5 trial design



KarXT dose is expressed as xanomeline/trospium.
[a]Washout of prior oral lithium and/or antipsychotics. [b]Optional increase in dose based on tolerability determined by clinician. [c]A safety follow-up/end of trial visit occurred approximately 1 week after the early termination or end of treatment visit.
BID, twice daily; KarXT, xanomeline/trospium.

Results

- A total of 566 and 558 participants comprised the safety and mITT populations, respectively
- At baseline, the PANSS total score (mean±standard deviation [SD]) in the mITT population was 66.0±10.4 and the CGI-S score was 3.4±0.7, indicating mild or moderate schizophrenia[9] (**Table 1**)

Table 1. Baseline demographic and clinical characteristics (mITT population)

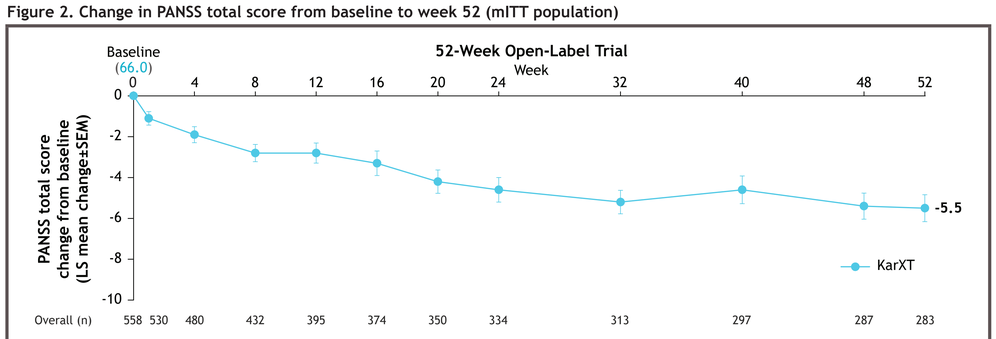
Parameter	Overall (N=558)
Age, years, mean±SD	47.4±11.8
Sex, n (%)	
Female	189 (33.9)
Male	369 (66.1)
Race, n (%)	
American Indian or Alaska Native	1 (0.2)
Asian	5 (0.9)
Black or African American	383 (68.6)
Native Hawaiian or other Pacific Islander	1 (0.2)
White	163 (29.2)
Unknown/other	5 (0.9)
Ethnicity, n (%)	
Hispanic or Latino	119 (21.3)
Not Hispanic or Latino	435 (78.0)
Not reported	4 (0.7)
PANSS total score, mean±SD	66.0±10.4
PANSS Marder positive factor score, mean±SD	20.2±4.2
PANSS Marder negative factor score, mean±SD	16.9±4.3
PANSS Marder uncontrolled hostility factor score, mean±SD	6.4±2.5
PANSS Marder disorganized thought factor score, mean±SD	15.0±3.5
PANSS Marder depression/anxiety factor score, mean±SD	7.5±3.2
CGI-S score, mean±SD	3.4±0.7

CGI-S, Clinical Global Impression-Severity; mITT, modified intention-to-treat; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

PANSS total score change from baseline to week 52

- Participants experienced a least squares (LS) mean change from baseline in PANSS total score of -5.5 points, indicating sustained efficacy with long-term KarXT treatment (**Figure 2**)

Figure 2. Change in PANSS total score from baseline to week 52 (mITT population)

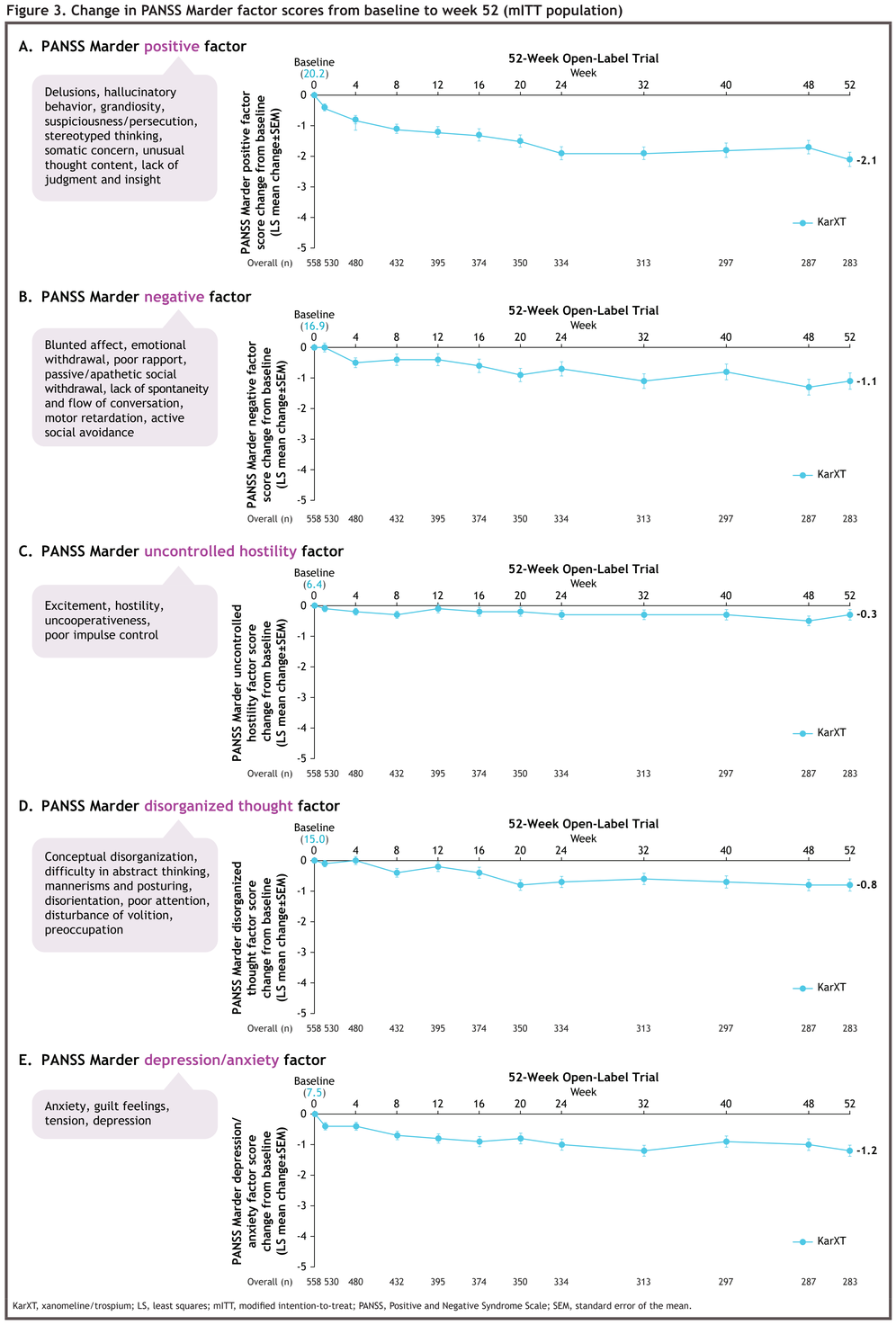


KarXT, xanomeline/trospium; LS, least squares; mITT, modified intention-to-treat; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

PANSS Marder factor change from baseline to week 52

- In post hoc analyses, long-term KarXT treatment resulted in mild reductions in PANSS Marder positive, negative, uncontrolled hostility, disorganized thought, and depression/anxiety factor scores (**Figure 3**)
  - The largest change was observed in the PANSS Marder positive factor score, which showed a 2.1-point reduction in LS mean at week 52
  - Long-term treatment with KarXT was associated with decreases in all individual PANSS item scores, except for stereotyped thinking, hostility, and disturbed volition, which were unchanged (data not shown)

Figure 3. Change in PANSS Marder factor scores from baseline to week 52 (mITT population)



KarXT, xanomeline/trospium; LS, least squares; mITT, modified intention-to-treat; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

Safety and tolerability

- A total of 82.3% of participants reported ≥1 TEAE, with 7.2% reporting ≥1 serious TEAE (**Table 2**)
  - The most common TEAEs were cholinergic in nature and included nausea, vomiting, and constipation
  - No new safety or tolerability concerns were reported

Table 2. Overall summary of long-term safety and tolerability (safety population)

Variable, n (%)	Overall (N=566)
Any TEAE	466 (82.3)
Any serious TEAE	41 (7.2)
Any TEAE leading to discontinuation	100 (17.7)
TEAEs occurring in ≥5% of people	
Nausea	131 (23.1)
Vomiting	115 (20.3)
Constipation	102 (18.0)
Diarrhea	53 (9.4)
Dry mouth	53 (9.4)
Dyspepsia	41 (7.2)
Dizziness	50 (8.8)
Headache	46 (8.1)
Somnolence	35 (6.2)
Weight decrease	32 (5.7)
Weight increase	10 (1.8)
Prolactin increase	3 (0.5)
TEAE of akathisia	7 (1.2)
TEAE of tardive dyskinesia	2 (0.4)
TEAE of dyskinesia	1 (0.2)

TEAE, treatment-emergent adverse event.

Conclusions

- KarXT is an approved treatment for schizophrenia in adults that exhibits no direct D_2 receptor binding.[9] Treatment with KarXT was associated with a numerical reduction in PANSS total score in the 52-week EMERGENT-5 trial
- Post hoc analysis of data from the EMERGENT-5 trial demonstrated mild and sustained reductions in PANSS Marder positive, negative, uncontrolled hostility, disorganized thought, and depression/anxiety factor scores in adults with schizophrenia with stable symptoms who were treated with KarXT
- These results supplement previous findings from the EMERGENT-5 trial showing long-term improvements in PANSS total, positive, and negative scores with KarXT treatment and indicate a sustained efficacy of KarXT across a range of symptoms in an outpatient population of adults with schizophrenia who are psychiatrically stable

Plain Language Summary

People living with schizophrenia have different types of symptoms that can be grouped into 5 categories: positive symptoms, negative symptoms, uncontrolled hostility, disorganized thought, and depression/anxiety. In this trial, adults with stable mild to moderate schizophrenia were switched from treatments that act on the dopamine systems in the brain to KarXT for 52 weeks to determine how well KarXT works in the long term. Participants treated with KarXT showed small and consistent score improvements in all symptom categories. As shown in earlier research, the most common side effects were related to KarXT treatment and generally did not cause trial participants to stop taking the medication. Overall, these results show that KarXT works well for treating symptoms of schizophrenia and has manageable side effects.

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Declaration of interests

TH has participated in speakers bureaus for Alkermes, ITCI, Neurocrine, and Teva. **JMK** has been a consultant for or received honoraria from Alkermes, Allergan, Boehringer-Ingelheim, Bristol Meyers Squibb, Cerevel, Click Therapeutics, Dainippon Sumitomo, Eli Lilly, H. Lundbeck, Intracellular Therapies, Janssen Pharmaceutica, Johnson and Johnson, Karuna, LB Pharmaceuticals, Mapi Pharma, Maplight, Merck, Minerva, Neurocrine, Newron, NW Pharmatech, Otsuka, Reviva, Roche, Sunovion, Takeda, and Teva. He has received grant support from Janssen, Lundbeck, Otsuka, and Sunovion. He has participated in advisory boards for Alkermes, Dainippon Sumitomo, Intracellular Therapies, Lundbeck, Neurocrine, Otsuka, Pierre Fabre, Takeda, and Teva. He is a Shareholder in Health Rhythms, LB Pharmaceuticals, Inc., Medincell, North Shore Therapies, and Vanguard Research Group. **JA**, **ME**, and **PN** are employees of Bristol Myers Squibb. **AC** was an employee of Bristol Myers Squibb at the time the analysis was conducted. **LS** is a member of speakers bureaus for Axsome, Bristol Myers Squibb, and Johnson and Johnson, and has participated in advisory boards for Bristol Myers Squibb and Boehringer-Ingelheim.

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