Safety and Efficacy of KarXT (Xanomeline–Trospium) in Patients With Schizophrenia: Results From a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial (EMERGENT-2)

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Background

- KarXT combines the dual M_1/M_4 preferring muscarinic receptor agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium
- In the 5-week, randomized, double-blind, placebo-controlled, phase 2 EMERGENT-1 trial (NCT03697252), 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 efficacy measures, and was generally well tolerated[1]

Methods

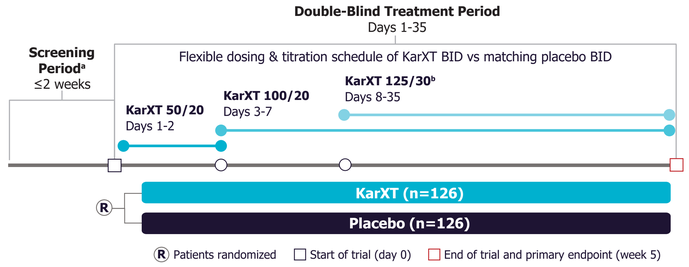
- EMERGENT-2 (NCT04659161) was a phase 3, randomized, double-blind, placebo-controlled, 5-week trial of KarXT vs placebo (**Figure 1**)
- Adult patients aged 18-65 years with a confirmed *DSM-5* diagnosis of schizophrenia and a recent worsening of psychotic symptoms warranting hospitalization were enrolled
- Eligible patients were randomized 1:1 to KarXT or matched placebo
- Dosing of KarXT (xanomeline/trospium) started at 50 mg/20 mg twice daily (BID) and increased to a maximum dose of 125 mg/30 mg BID
- Primary efficacy endpoint: change from baseline to week 5 in PANSS total score compared with placebo
- Secondary efficacy endpoints: change from baseline to week 5 in PANSS positive subscale, PANSS negative subscale, and PANSS Marder negative factor subscale scores; Clinical Global Impression–Severity (CGI-S) score at week 5; and percentage of PANSS responders at week 5[a]

Statistical Analyses

- Efficacy analyses were performed in the modified intent-to-treat population, defined as all randomized patients who received ≥1 dose of study medication, had a baseline PANSS assessment, and had ≥1 postbaseline PANSS assessment
- Safety analyses were performed in the safety population, defined as all patients who received ≥1 dose of study drug

[a]Analysis is ongoing and results to be presented at a future meeting.

Figure 1. EMERGENT-2 Trial Design



KarXT dose is expressed as xanomeline/trospium (mg/mg). [a]Washout of prior oral lithium and/or antipsychotics. [b]Optional increase in dose based on tolerability determined by a clinician. BID, twice daily.

Results

- A total of 252 patients at 22 study sites in the United States were enrolled
- There were no meaningful differences in baseline demographics and characteristics between treatment groups (**Table 1**)

Table 1. Baseline Demographics and Characteristics (ITT Population)

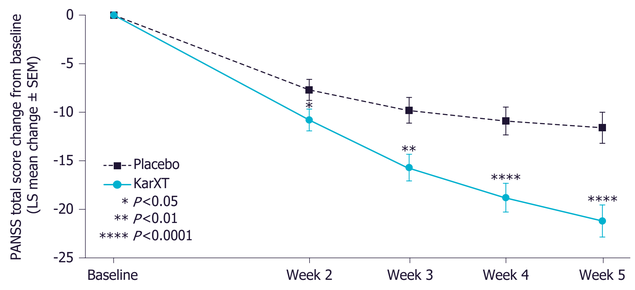
	KarXT (n=126)	Placebo (n=126)
Mean age, years (SD)	45.6 (10.4)	46.2 (10.8)
Sex, n (%)		
Male	95 (75.4)	95 (75.4)
Female	31 (24.6)	31 (24.6)
Race, n (%)		
Asian	2 (1.6)	1 (0.8)
Black	97 (77.0)	92 (73.0)
White	26 (20.6)	31 (24.6)
Other	1 (0.8)	2 (1.6)
PANSS total score, mean (SD)	98.3 (8.9)	97.9 (9.7)
PANSS positive subscale score, mean (SD)	26.8 (3.7)	26.7 (4.0)
PANSS negative subscale score, mean (SD)	22.9 (4.0)	22.9 (3.8)
PANSS Marder negative factor subscale score, mean (SD)	22.9 (5.0)	22.5 (4.7)

ITT defined as all randomized patients.
ITT, intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Primary Endpoint: Change in PANSS Total Score vs Placebo at Week 5

- KarXT demonstrated a statistically significant and clinically meaningful 9.6-point reduction in PANSS total score compared with placebo at week 5 (-21.2 KarXT vs -11.6 placebo, $P<0.0001$; Cohen's d effect size=0.61) (**Figure 2**)
- KarXT demonstrated a statistically significant improvement in PANSS total score starting at week 2 (first postbaseline rating) and maintained such improvement through all time points in the trial

Figure 2. Change From Baseline in PANSS Total Score vs Placebo at Week 5

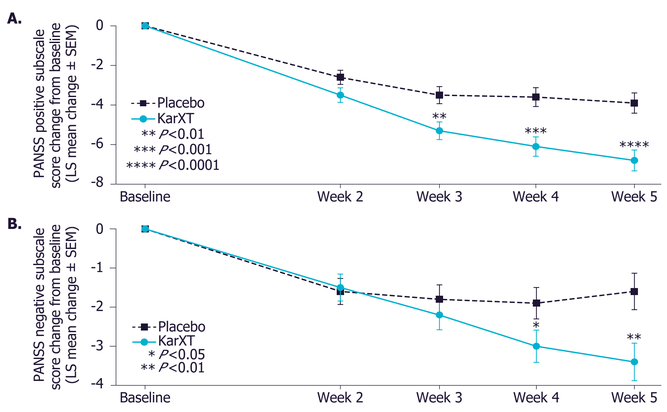


LS, least squares; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

Secondary Endpoints

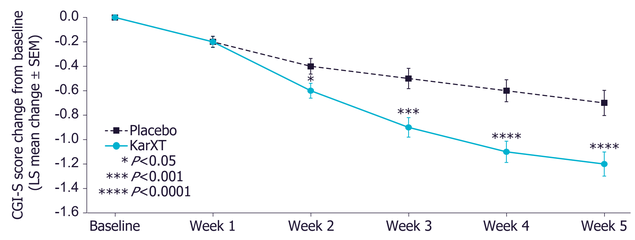
- KarXT demonstrated a statistically significant reduction in PANSS positive and negative subscale scores (**Figure 3**) and CGI-S score (**Figure 4**) compared with placebo
- A significantly greater proportion of patients in the KarXT arm had a ≥30% reduction in PANSS total score compared with placebo starting at week 3 and continuing through the study end (**Figure 5**)

Figure 3. Change From Baseline in (A) PANSS Positive Subscale Score and (B) PANSS Negative Subscale Score



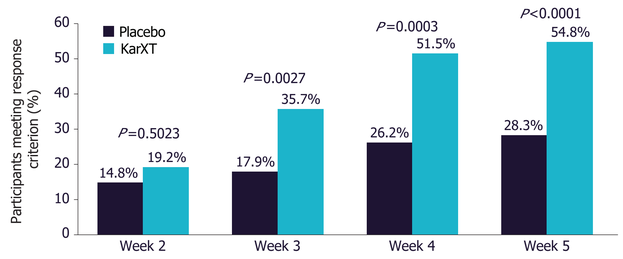
LS, least squares; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

Figure 4. Change From Baseline in CGI-S Score vs Placebo at Week 5



The difference between KarXT and placebo at week 5 is estimated using mixed model for repeated measures.
CGI-S, Clinical Global Impression–Severity; LS, least squares; SEM, standard error of the mean.

Figure 5. PANSS ≥30% Categorical Response by Study Week



Floor-adjusted total score (total score-30).
PANSS, Positive and Negative Syndrome Scale.

Safety and Tolerability

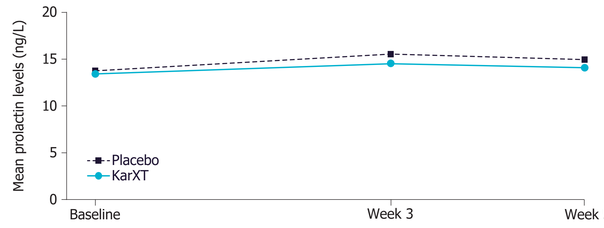
- KarXT was generally well tolerated (**Table 2**), with a side effect profile substantially consistent with prior trials
- Overall discontinuation rates were similar between KarXT and placebo arms (25% vs 21%)
- Common treatment-emergent adverse events (TEAEs; ≥5%) were all mild to moderate in severity and mostly transient in nature
- KarXT was not associated with Parkinsonism, dystonia, akathisia, or sedation, which are common AEs of current antipsychotic medications
- Prolactin levels were similar between treatment groups over the 5-week treatment period (mean change from baseline to week 5: KarXT, 1.0 ± 9.27 ng/L; placebo, 0.8 ± 9.59 ng/L) (**Figure 6**)

Table 2. Safety and Tolerability During the 5-Week Treatment Period (Safety Population)

Variable	KarXT (n=126)	Placebo (n=125)
Any TEAE, n (%)	95 (75.4)	73 (58.4)
Serious TEAE,[a] n (%)	2 (1.6)	2 (1.6)
TEAE leading to discontinuation, n (%)	9 (7.1)	7 (5.6)
TEAE occurring in ≥5% of patients in the KarXT group, n (%)		
Constipation	27 (21.4)	13 (10.4)
Dyspepsia	24 (19.0)	10 (8.0)
Nausea	24 (19.0)	7 (5.6)
Vomiting	18 (14.3)	1 (0.8)
Headache	17 (13.5)	15 (12.0)
Hypertension[b]	12 (9.5)	1 (0.8)
Dizziness	11 (8.7)	4 (3.2)
Gastroesophageal reflux disease	8 (6.3)	0 (0)
Abdominal discomfort	7 (5.6)	4 (3.2)
Diarrhea	7 (5.6)	4 (3.2)
Mean change from baseline to week 5 in Simpson-Angus Scale score, ± SD	0.0 ± 0.61	-0.1 ± 0.70
Mean change from baseline to week 5 in Barnes Akathisia Rating Scale score, ± SD	-0.1 ± 1.09	-0.2 ± 0.98

[a]Serious TEAEs were 2 cases of suicidal ideation in the KarXT group, 1 case of appendicitis in the placebo group, and 1 case of worsening of schizophrenia in the placebo group.
[b]Hypertension is the MedDRA preferred term and is not necessarily reflective of clinical hypertension.
MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation; TEAE, treatment-emergent adverse event.

Figure 6. Prolactin Levels



Prolactin reference range: males <20 ng/mL, nonpregnant females <25 ng/mL.

Conclusions

- In the phase 3 EMERGENT-2 study, KarXT demonstrated a statistically significant and clinically meaningful improvement in PANSS total score vs placebo starting at week 2, which was maintained through all time points in the trial
- KarXT also met tested secondary endpoints, demonstrating a statistically significant reduction in both positive and negative symptoms of schizophrenia and the proportion of patients achieving PANSS responder criteria vs placebo
- Consistent with prior trials, KarXT was generally well tolerated. The most common TEAEs were all mild to moderate in severity and mostly cholinergic in nature
- KarXT was not associated with common problematic side effects of currently available antipsychotics, including somnolence, prolactin elevation, or extrapyramidal/motor symptoms
- KarXT has the potential to be the first in a new class of treatments for patients with schizophrenia based on muscarinic receptor agonism

Reference

1. Brannan SK, et al. *N Engl J Med.* 2021;384(8):717-726.

Disclosures

CUC has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo Pharma, Boehringer Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Gedeon Richter, Hikma, Holmusk, Intra-Cellular Therapies, Janssen/Johnson & Johnson, Karuna Therapeutics, LB Pharma, Lundbeck, MedAvante-ProPhase, MedinCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine Biosciences, Newron, Noven, Otsuka, Pharmabrain, PPD, Recordati, Relmada, Reviva, ROVI, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris; provided expert testimony for Janssen and Otsuka; served on a data safety monitoring board for Lundbeck, Relmada, Reviva, ROVI, Supernus, and Teva; has received grant support from Janssen and Takeda; received royalties from UpToDate; and is a stock option holder of Cardio Diagnostics, Mindpax, and LB Pharma. SMP, ASA, IK, and SKB are employees of and hold equity in Karuna Therapeutics.

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