Safety and Efficacy of KarXT in Patients With Schizophrenia in the Randomized, Double-Blind, Placebo-Controlled, Phase 3 EMERGENT-2 and EMERGENT-3 Trials

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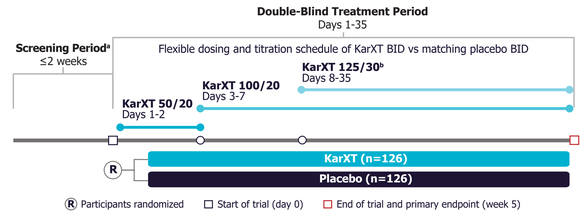
Introduction

- KarXT combines the dual M_1/M_4 preferring muscarinic receptor agonist xanomeline and the peripherally restricted anticholinergic trospium chloride with the goal of preserving the beneficial central nervous system effects of xanomeline while ameliorating the cholinergic adverse events (AEs) due to peripheral muscarinic receptor activation[1]
- In the 5-week, randomized, double-blind, placebo-controlled, inpatient phase 2 EMERGENT-1 trial (NCT03697252),[2] KarXT met the primary endpoint of a significant reduction in Positive and Negative Syndrome Scale (PANSS) total score at week 5 compared with placebo, improved other key prespecified secondary outcomes measures, and was generally well tolerated

Methods

- EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) were 2 identical, 5-week, randomized, double-blind, inpatient phase 3 trials of KarXT vs placebo in adults with schizophrenia and a recent worsening of psychotic symptoms warranting hospitalization (**Figure 1**)
  - Dosing of KarXT (mg xanomeline/mg trospium) started with 50 mg/20 mg twice daily (BID) and increased to a maximum of 125 mg/30 mg BID by the end of week 1
- The primary efficacy endpoint was mean change from baseline to week 5 in PANSS total score compared with placebo
- Key prespecified secondary outcomes measures included mean change from baseline to week 5 in PANSS positive subscale, PANSS negative subscale, and PANSS Marder negative factor scores
- Efficacy analyses were performed in the modified intent-to-treat population, defined as all randomized participants who received ≥1 dose of trial medication, had a baseline PANSS assessment, and had ≥1 postbaseline PANSS assessment
- Safety analyses were performed in the safety population, defined as all participants who received ≥1 dose of trial drug

Figure 1. EMERGENT-2 and EMERGENT-3 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 clinician. BID, twice daily.

Results

Participants

- A total of 252 people were enrolled in EMERGENT-2 and 256 people were enrolled in EMERGENT-3
- There were no meaningful differences in baseline demographics and characteristics between treatment groups in each trial (**Table 1**)

Table 1. Baseline Demographics and Characteristics (ITT Population)

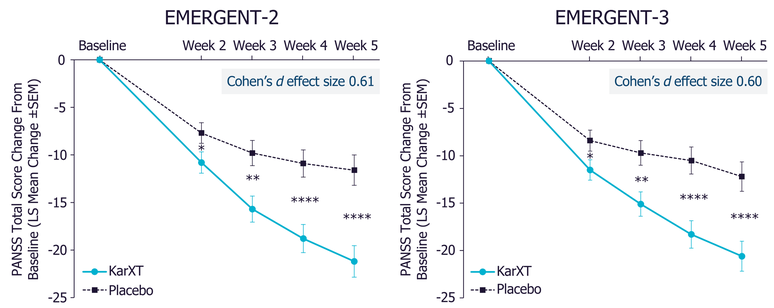
	EMERGENT-2		EMERGENT-3	
	KarXT (n=126)	Placebo (n=126)	KarXT (n=125)	Placebo (n=131)
Mean age, years (SD)	45.6 (10.4)	46.2 (10.8)	43.6 (11.4)	42.6 (12.2)
Sex, n (%)				
Male	95 (75.4)	95 (75.4)	87 (69.6)	104 (79.4)
Female	31 (24.6)	31 (24.6)	38 (30.4)	27 (20.6)
Race, n (%)				
Asian	2 (1.6)	1 (0.8)	1 (0.8)	0
Black	97 (77.0)	92 (73.0)	79 (63.2)	77 (58.8)
White	26 (20.6)	31 (24.6)	45 (36.0)	53 (40.5)
Other	1 (0.8)	2 (1.6)	0	0
Not reported	0	0	0	1 (0.8)
PANSS total score, mean (SD)	98.3 (8.9)	97.9 (9.7)	97.3 (8.9)	96.7 (8.9)
PANSS positive subscale score, mean (SD)	26.8 (3.7)	26.7 (4.0)	26.9 (3.7)	26.4 (3.3)
PANSS negative subscale score, mean (SD)	22.9 (4.0)	22.9 (3.8)	22.6 (3.2)	22.0 (3.7)
PANSS Marder negative factor score, mean (SD)	22.9 (5.0)	22.5 (4.7)	22.0 (3.7)	21.8 (4.2)

ITT defined as all randomized participants.
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

- In both trials, KarXT demonstrated a statistically significant and clinically meaningful improvement in PANSS total score vs placebo starting at week 2 (first postbaseline rating) and maintained such improvement through all time points (**Figure 2**)

Figure 2. Change From Baseline to Week 5 in PANSS Total Score

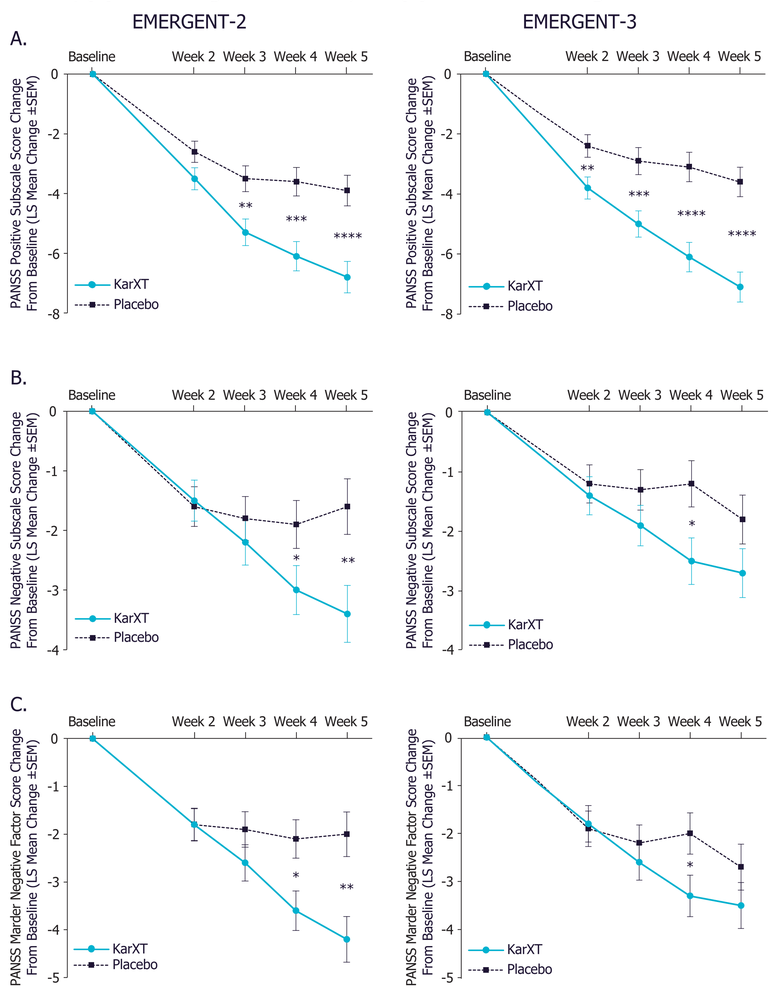


*P<0.05; **P<0.01; ****P<0.0001.
LS, least squares; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

Key Prespecified Secondary Outcomes Measures

- In both trials, KarXT was associated with a statistically significant improvement in PANSS positive subscale score vs placebo starting at week 2 (first postbaseline rating), which was maintained through the trial end (**Figure 3A**)
- KarXT was associated with a statistically significant improvement in PANSS negative subscale (**Figure 3B**) and PANSS Marder negative factor scores at weeks 4 and 5 in EMERGENT-2 and week 4 in EMERGENT-3 (**Figure 3C**)

Figure 3. Change From Baseline to Week 5 in PANSS Total Score in (A) PANSS Positive Subscale, (B) PANSS Negative Subscale, and (C) PANSS Marder Negative Factor Scores



*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.
LS, least squares; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

Safety and Tolerability

- In both trials, KarXT was generally well tolerated (**Table 2**)
- Overall discontinuation rates were 23% in EMERGENT-2 (25%, KarXT; 21%, placebo) and 33% in EMERGENT-3 (37%, KarXT; 29%, placebo)
- Discontinuation rates due to treatment-emergent AEs (TEAEs) were similar between treatment arms
- The most common TEAEs (≥5% in KarXT group) were all mild to moderate in severity and mostly transient in nature
- Commonly reported cholinergic TEAEs mostly occurred within the first 2 weeks of treatment and were generally transient in nature

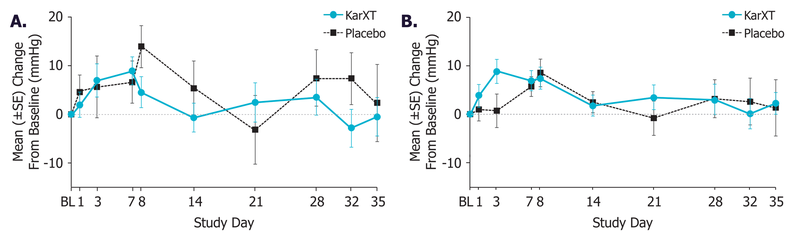
Table 2. Safety and Tolerability During the 5-Week Treatment Period (Safety Population)

Variable	EMERGENT-2		EMERGENT-3	
	KarXT (n=126)	Placebo (n=125)	KarXT (n=125)	Placebo (n=128)
Any TEAE, n (%)	95 (75.4)	73 (58.4)	88 (70.4)	64 (50.0)
Serious TEAE,[a,b] n (%)	2 (1.6)	2 (1.6)	1 (0.8)	0
TEAE leading to discontinuation, n (%)	9 (7.1)	7 (5.6)	8 (6.4)	7 (5.5)
TEAE occurring in ≥5% of people in the KarXT group in either trial, n (%)				
Constipation	27 (21.4)	13 (10.4)	16 (12.8)	5 (3.9)
Dyspepsia	24 (19.0)	10 (8.0)	20 (16.0)	2 (1.6)
Nausea	24 (19.0)	7 (5.6)	24 (19.2)	2 (1.6)
Vomiting	18 (14.3)	1 (0.8)	20 (16.0)	1 (0.8)
Headache	17 (13.5)	15 (12.0)	14 (11.2)	15 (11.7)
Hypertension[c]	12 (9.5)	1 (0.8)	8 (6.4)	2 (1.6)
Dizziness	11 (8.7)	4 (3.2)	2 (1.6)	1 (0.8)
Gastroesophageal reflux disease	8 (6.3)	0	5 (4.0)	1 (0.8)
Abdominal discomfort	7 (5.6)	4 (3.2)	2 (1.6)	3 (2.3)
Diarrhea	7 (5.6)	4 (3.2)	7 (5.6)	1 (0.8)
Insomnia	3 (2.4)	6 (4.8)	7 (5.6)	10 (7.8)
Body weight: mean change from baseline to week 5, kg±SD	1.36±3.31	2.49±6.92	1.41±3.37	2.0±3.08
Body weight: ≥7% increase from baseline to week 5, n/N (%)	6/94 (6.4)	13/100 (13.0)	5/78 (6.4)	12/92 (13.0)
Simpson-Angus Scale score: mean change from baseline to week 5, ±SD	0.0±0.61	-0.1±0.70	-0.1±0.56	-0.1±0.36
Barnes Akathisia Rating Scale score: mean change from baseline to week 5, ±SD	-0.1±1.09	-0.2±0.98	-0.1±0.75	-0.1±0.88

[a]In EMERGENT-2, 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]In EMERGENT-3, 1 serious TEAE of gastroesophageal reflux disease occurred in the KarXT group. [c]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.

- Mean blood pressure change from baseline was similar between KarXT and placebo
- An increased heart rate was associated with KarXT treatment and decreased in magnitude by the end of both trials
- No cases of syncope were observed
- Measures of weight gain, somnolence, and extrapyramidal/motor symptoms were similar between KarXT and placebo

Figure 4. Change in Supine (A) Systolic and (B) Diastolic Blood Pressure in Participants With a TEAE of Hypertension: Combined Results From EMERGENT-1, EMERGENT-2, and EMERGENT-3



During treatment, beginning on day 1, blood pressure was measured 2 (±1) hours after morning dose of trial treatment.
BL, baseline; SE, standard error; TEAE, treatment-emergent adverse event.

Conclusions

- In the phase 3 EMERGENT-2 and EMERGENT-3 trials, KarXT demonstrated a consistent, statistically significant, clinically meaningful improvement in PANSS total score vs placebo starting at week 2, which was maintained through all time points in the trial
- In both trials, KarXT was associated with a significantly greater improvement in PANSS positive subscale score at week 5 compared with placebo
- Improvement in PANSS negative subscale and PANSS Marder negative factor scores at week 5 with KarXT achieved statistical significance compared with placebo only in EMERGENT-2
- Consistent with prior trials, KarXT was generally well tolerated and not associated with common problematic side effects of currently available antipsychotics, including weight gain, somnolence, or extrapyramidal/motor symptoms

References

1. Paul SM, et al. *Am J Psychiatry.* 2022;179(9):611-627.
2. Brannan SK, et al. *N Engl J Med.* 2021;384(8):717-726.

Disclosures

SKB is an employee of and holds equity in Karuna Therapeutics.

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