Efficacy of KarXT (Xanomeline–Trospium) in Schizophrenia: Pooled Results From the Randomized, Double-Blind, Placebo-Controlled EMERGENT Trials

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Introduction

- KarXT (xanomeline–trospium chloride) is a potential new treatment for people with schizophrenia with a novel mechanism of action based on muscarinic receptor agonism
- In the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252),[1] EMERGENT-2 (NCT04659161),[2] and EMERGENT-3 (NCT04738123)[3] trials, KarXT significantly improved psychotic symptoms compared with placebo as measured by change in Positive and Negative Syndrome Scale (PANSS) total score at week 5 and was generally well tolerated in people with schizophrenia experiencing acute psychosis

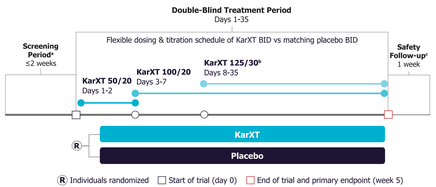
Objective

- To evaluate the efficacy of KarXT for the treatment of acute psychosis in people with schizophrenia using pooled data from the EMERGENT trials

Methods

- EMERGENT-1, EMERGENT-2, and EMERGENT-3 were 5-week, randomized, double-blind, placebo-controlled trials of KarXT of similar design (**Figure 1**)
- The trials enrolled people aged 18-60 years (EMERGENT-1) or 18-65 years (EMERGENT-2 and EMERGENT-3) with a confirmed *DSM-5* diagnosis of schizophrenia and a recent worsening of psychosis warranting hospitalization
- Participants were required to have a PANSS total score ≥80 and Clinical Global Impression–Severity (CGI-S) score ≥4
- EMERGENT-1 and EMERGENT-2 enrolled participants from the United States and EMERGENT-3 enrolled participants from the United States and Ukraine
- Eligible participants were randomized 1:1 to receive oral KarXT or matched placebo twice daily (BID) for 5 weeks
  - Dosing of KarXT (xanomeline/trospium) started with 50 mg/20 mg BID and increased to a maximum of 125 mg/30 mg BID by the end of week 1
- In all 3 trials, the primary endpoint was change from baseline to week 5 in PANSS total score
- Other efficacy measures included change from baseline to week 5 in PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, and CGI-S scores
- Data from the EMERGENT trials were pooled, and all efficacy analyses were conducted in the modified intent-to-treat (mITT) population, defined as all randomized participants who received ≥1 trial drug dose and had a baseline and ≥1 postbaseline PANSS assessment

Figure 1. Trial Design



KarXT dose is expressed as xanomeline/trospium chloride (mg/mg).
[a]Washout of prior oral lithium and/or antipsychotics. [b]Optional increase in dose based on tolerability determined by clinician. [c]EMERGENT-2 and EMERGENT-3 only.
BID, twice daily.

Results

Participants

- A total of 640 participants (KarXT, n=314; placebo, n=326) were included in the mITT population used for pooled efficacy analyses
- There were no meaningful differences in baseline demographics and characteristics between treatment groups (**Table 1**)

Primary Endpoint: PANSS Total Score Change From Baseline to Week 5

- Across trials, KarXT was associated with a significantly greater improvement in PANSS total score from baseline to week 5 compared with placebo (KarXT, -19.4; placebo, -9.6 [least squares mean (LSM) difference, -9.9; 95% confidence interval (CI), -12.4 to -7.3; *P*<0.0001; Cohen's *d*, 0.65]) (**Figure 2**)

Secondary Outcomes Measures

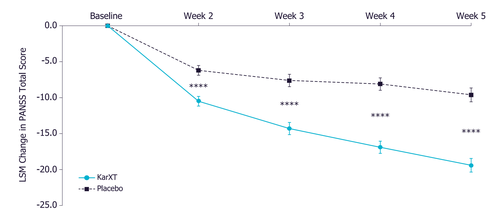
- Across trials, KarXT was associated with a significantly greater improvement from baseline to week 5 in other key secondary outcomes measures
  - PANSS positive subscale score: KarXT, -6.3; placebo, -3.1 (LSM difference, -3.2; 95% CI, -4.1 to -2.4; *P*<0.0001; Cohen's *d*, 0.67) (**Figure 3A**)
  - PANSS negative subscale score: KarXT, -3.0; placebo, -1.3 (LSM difference, -1.7; 95% CI, -2.4 to -1.0; *P*<0.0001; Cohen's *d*, 0.40) (**Figure 3B**)
  - PANSS Marder negative factor score: KarXT, -3.8; placebo, -1.8 (LSM difference, -2.0; 95% CI, -2.8 to -1.2; *P*<0.0001; Cohen's *d*, 0.42) (not shown)
  - CGI-S score: KarXT, -1.1; placebo, -0.5 (LSM difference, -0.6; 95% CI, -0.8 to -0.4; *P*<0.0001; Cohen's *d*, 0.63) (not shown)
- A higher proportion of participants in the KarXT group vs the placebo group had a ≥1-point improvement in CGI-S scale score starting at week 1 and continuing through the end of the trial (**Figure 4**)
- A significantly higher proportion of participants in the KarXT group vs the placebo group had a ≥20% (56.1% vs 33.4%; *P*<0.0001), ≥30% (41.4% vs 20.9%; *P*<0.0001), ≥40% (26.8% vs 14.1%; *P*<0.0001), and ≥50% (15.3% vs 8.3%; *P*<0.01) improvement from baseline to week 5 in PANSS total score (**Figure 5**)
  - A PANSS total score reduction of ≥20% is a standard measure of minimal clinically meaningful change, and a score reduction of ≥50% represents "much improved"[4]
  - A significantly higher proportion of participants in the placebo group vs the KarXT group had worsening of symptoms from baseline to week 5 in PANSS total score (21.8% vs 8.3%; *P*<0.0001)

Table 1. Baseline Demographics and Characteristics (mITT Population)

Parameter	KarXT (n=314)	Placebo (n=326)
Age (years), mean±SD	44.6±10.7	43.7±11.3
Sex, n (%)		
Male	233 (74.2)	250 (76.7)
Female	81 (25.8)	76 (23.3)
Race, n (%)		
Asian	4 (1.3)	2 (0.6)
Black	225 (71.7)	221 (67.8)
Native Hawaiian or other Pacific Islander	1 (0.3)	1 (0.3)
White	83 (26.4)	98 (30.1)
Other	1 (0.3)	4 (1.2)
Ethnicity, n (%)		
Hispanic or Latino	47 (15.0)	34 (10.4)
Not Hispanic or Latino	265 (84.4)	291 (89.3)
Not reported	2 (0.6)	1 (0.3)
Country, n (%)		
United States	295 (93.9)	300 (92.0)
Ukraine	19 (6.1)	26 (8.0)
Weight (kg), mean±SD	88.9±18.5	87.3±18.6
BMI (kg/m^2), mean±SD	29.2±5.5	28.9±5.4
PANSS total score, mean±SD	97.5±9.0	97.0±8.9
PANSS positive subscale score, mean±SD	26.6±3.6	26.4±3.4
PANSS negative subscale score, mean±SD	22.7±3.8	22.6±4.0
PANSS Marder negative factor, mean±SD	22.4±4.5	22.3±4.6
CGI-S score, mean±SD	5.1±0.6	5.0±0.6

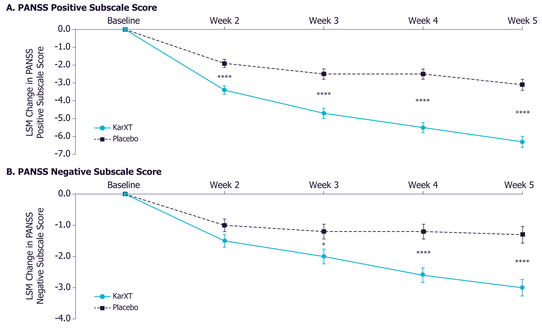
BMI, body mass index; CGI-S, Clinical Global Impression–Severity; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Figure 2. PANSS Total Score Change From Baseline



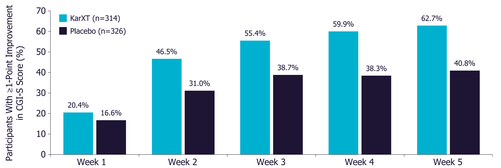
****P<0.0001.
Values are LSM change±standard error.
LSM, least squares mean; PANSS, Positive and Negative Syndrome Scale.

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



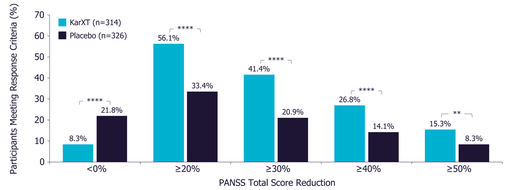
*P<0.05. ****P<0.0001. Values are LSM change±standard error.
LSM, least squares mean; PANSS, Positive and Negative Syndrome Scale.

Figure 4. Proportion of Participants Achieving ≥1-Point Improvement in CGI-S Score Over Time



Participants who discontinued early or had missing data at a given time point are imputed using the last observation carried forward.
CGI-S, Clinical Global Impression–Severity.

Figure 5. PANSS Categorical Response Rates at Week 5



**P<0.01, ****P<0.0001. Based on floor-adjusted total score (total score minus 30); participants who discontinued early or had missing data at a given time point are imputed using the last observation carried forward.
PANSS, Positive and Negative Syndrome Scale.

Conclusions

- In pooled analyses from the EMERGENT trials, KarXT demonstrated statistically significant improvements across efficacy measures, with consistent and robust effect sizes
- If approved, these findings support the potential of KarXT to be first in a new class of medications to treat schizophrenia based on muscarinic receptor agonism and without direct dopamine D_2 receptor blocking activity

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Disclosures

IK, SS, JK, ACM, SMP, and SKB are employees of and hold equity in Karuna Therapeutics. LC is a consultant for AbbVie/Allergan, Acadia, Adamas, Alkermes, Angelini, Astellas, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, Impel, INmune Bio, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Lyndra, Marvin, MedAvante-ProPhase, Merck, Mitsubishi-Tanabe Pharma, Neurelis, Neurocrine, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sunovion, Supernus, Teva, and University of Arizona and provides one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; a speaker for AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, and Teva and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and universities and professional organizations/societies; holds a small number of shares of common stock in Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Pfizer (purchased >10 years ago) and stock options in Reviva; and receives royalties/publishing income royalties from Taylor & Francis (Editor-in-Chief, *Current Medical Opinion*, 2022-2023), Wiley (Editor-in-Chief, *International Journal of Clinical Practice*, through end 2019), *UpToDate* (reviewer), *Springer Healthcare* (book), and Elsevier (Topic Editor, *Psychiatry*; *Clinical Therapeutics*).

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