Categorical Response Rates, Time Course of Response, and Symptom Domains of Response With KarXT (Xanomeline–Trospium) in the EMERGENT-3 Trial

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Introduction

- The efficacy and tolerability limitations of currently available antipsychotics, all of which have direct D_2 dopamine receptor blocking activity, are well known[1,2]; a substantial unmet need remains for more effective, better tolerated treatments for schizophrenia with novel mechanisms of action
- KarXT combines the dual M_1/M_4 preferring muscarinic receptor agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride with the goal of preserving the beneficial effects of xanomeline in the central nervous system while ameliorating side effects due to peripheral muscarinic receptor activation
- In the 5-week, randomised, double-blind, placebo-controlled EMERGENT-1 (NCT03697252),[3] EMERGENT-2 (NCT04659161),[4] and EMERGENT-3 (NCT04738123)[5] trials, KarXT significantly improved 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 assess the effect of KarXT on PANSS categorical response rates, time course of response, and symptom domains of response in people with schizophrenia enrolled in EMERGENT-3

Methods

- EMERGENT-3 was a randomised, double-blind, placebo-controlled, inpatient, phase 3 trial of KarXT in people with schizophrenia with acute psychosis
- Eligible participants were randomised 1:1 to receive oral KarXT or matched placebo twice daily (BID) for 5 weeks
  - Dosing of KarXT (mg xanomeline/mg 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
- Categorical thresholds of response assessed were PANSS total score reductions from baseline of ≥20%, ≥30%, ≥40%, and ≥50% at weeks 2, 3, 4, and 5
  - The proportion of participants with ≥30% reduction in PANSS total score at week 5 was a prespecified secondary outcome measure
  - Number needed to treat (NNT) was calculated for each categorical threshold at week 5
- A Marder 5-factor model of the PANSS[6] was used to assess symptom subdomains of response (positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression)

Statistical Analyses

- Analyses were performed in the modified intention-to-treat (mITT) population, defined as all randomised participants who received ≥1 dose of trial medication and had a baseline and ≥1 postbaseline PANSS assessment
- For all PANSS categorical response analyses, PANSS items were rescaled from a range of 1-7 to 0-6 and floor adjusted by subtracting 30 points from baseline and postbaseline scores
- Logistic regression models were used to compare PANSS response rates in each treatment group, adjusting for factors of age, sex, and treatment group
- NNT for each threshold at week 5 was calculated as 1 divided by the difference in PANSS responder rates for KarXT and placebo
- Change from baseline in the 5 PANSS Marder factors was analysed using mixed model for repeated measures, with the observed change from baseline at each visit as the response, including treatment group, visit, and the interaction of treatment group and visit as fixed effects and baseline score, site, age, and sex as covariates

Results

Participants

- Of 234 randomised participants meeting mITT criteria, 114 were in the KarXT group and 120 in the placebo group
- Mean PANSS total scores (±standard deviation) at baseline were 96.9±8.75 and 96.5±8.81 points in the KarXT and placebo groups, respectively

Categorical Response Rate

- At week 5, KarXT-treated participants meeting the categorical response rate criteria ranged from 57.0% (n=65) for the ≥20% threshold to 13.2% (n=15) for the ≥50% threshold (**Figure 1**)
- Corresponding NNTs for achieving a PANSS response at week 5 ranged from 6 for the ≥20% threshold to 18 for the ≥50% threshold

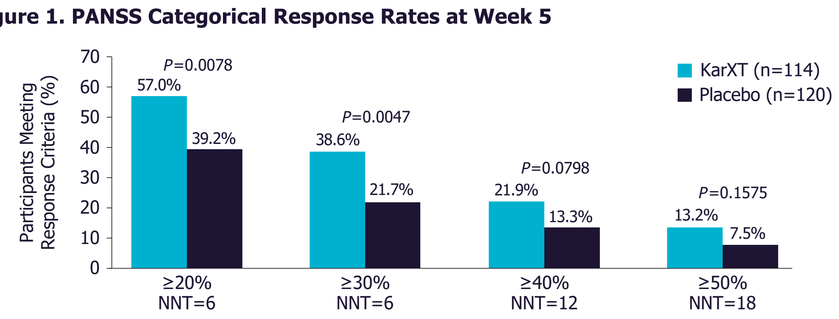
Time Course of Response

- PANSS response rates were significantly higher with KarXT vs placebo (P<0.05) starting at week 4 for the ≥20% and ≥30% thresholds and at week 3 for the ≥40% threshold; the ≥50% threshold was significantly higher with KarXT vs placebo only at week 4 (**Figure 2**)

PANSS Marder 5-Factor Response

- The KarXT group was associated with statistically significantly greater improvement from baseline to week 5 vs the placebo group on the PANSS Marder positive, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression factors; the PANSS Marder negative factor achieved statistical significance only at week 4 (**Table 1; Figure 3**)
- A statistically significantly greater improvement with KarXT vs placebo was observed starting at week 2 for the PANSS Marder positive factor and at week 3 for the PANSS Marder disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression factors (**Figure 3**)

Figure 1. PANSS Categorical Response Rates at Week 5



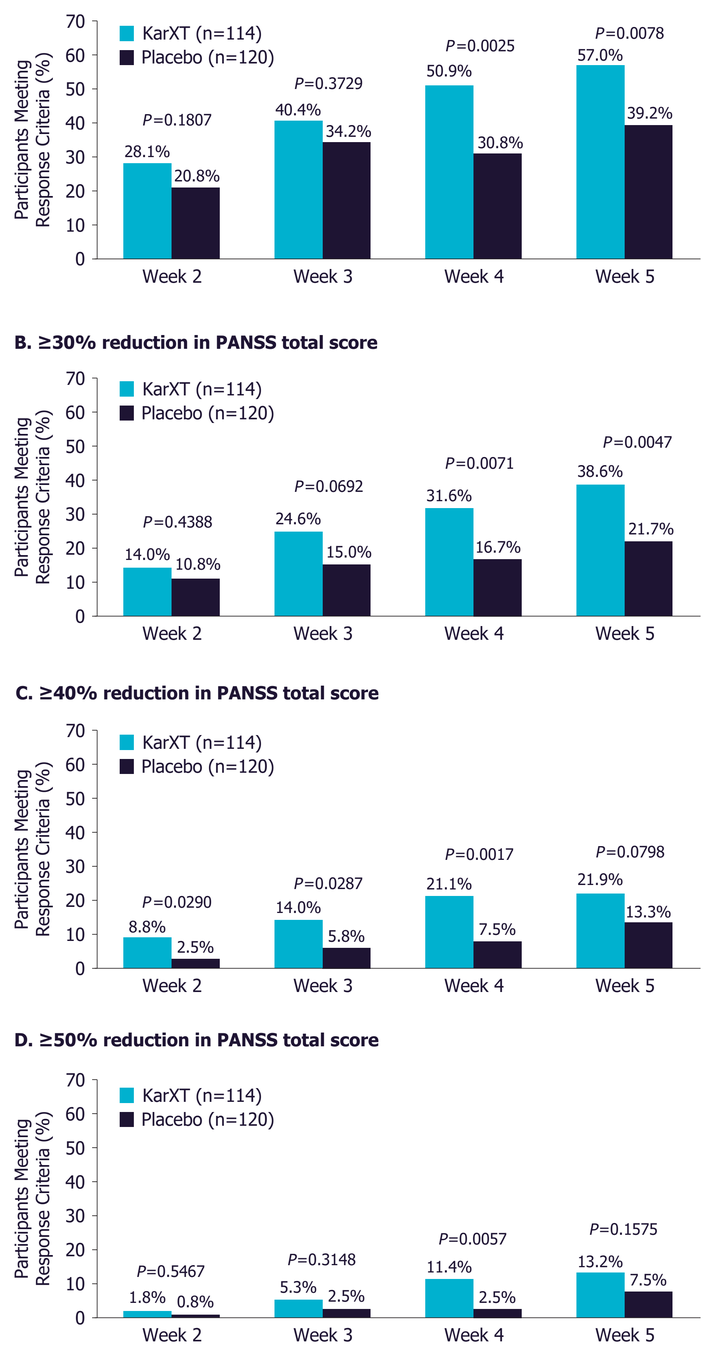
NNT, number needed to treat; PANSS, Positive and Negative Syndrome Scale.

Table 1. PANSS Marder 5-Factor Response by Treatment Assignment at Week 5

Marder Factor	Group	Baseline Score, Mean±SD	LSM Change From Baseline to Week 5[a]	Week 5 KarXT-Placebo LSM Difference	*P* Value	Cohen's *d*
Positive[b]	KarXT	30.5±3.80	-6.60	-2.64	0.0002	0.564
	Placebo	30.4±3.64	-3.96			
Negative[c]	KarXT	22.0±3.74	-3.48	-0.82	0.1957	0.194
	Placebo	21.9±4.15	-2.66			
Disorganised thoughts[d]	KarXT	22.0±3.50	-3.86	-1.37	0.0103	0.389
	Placebo	21.6±3.92	-2.49			
Uncontrolled hostility/excitement[e]	KarXT	10.1±3.22	-2.34	-1.69	0.0003	0.551
	Placebo	10.1±3.09	-0.65			
Anxiety/depression[f]	KarXT	12.3±3.30	-4.51	-1.57	0.0031	0.452
	Placebo	12.6±3.29	-2.94			

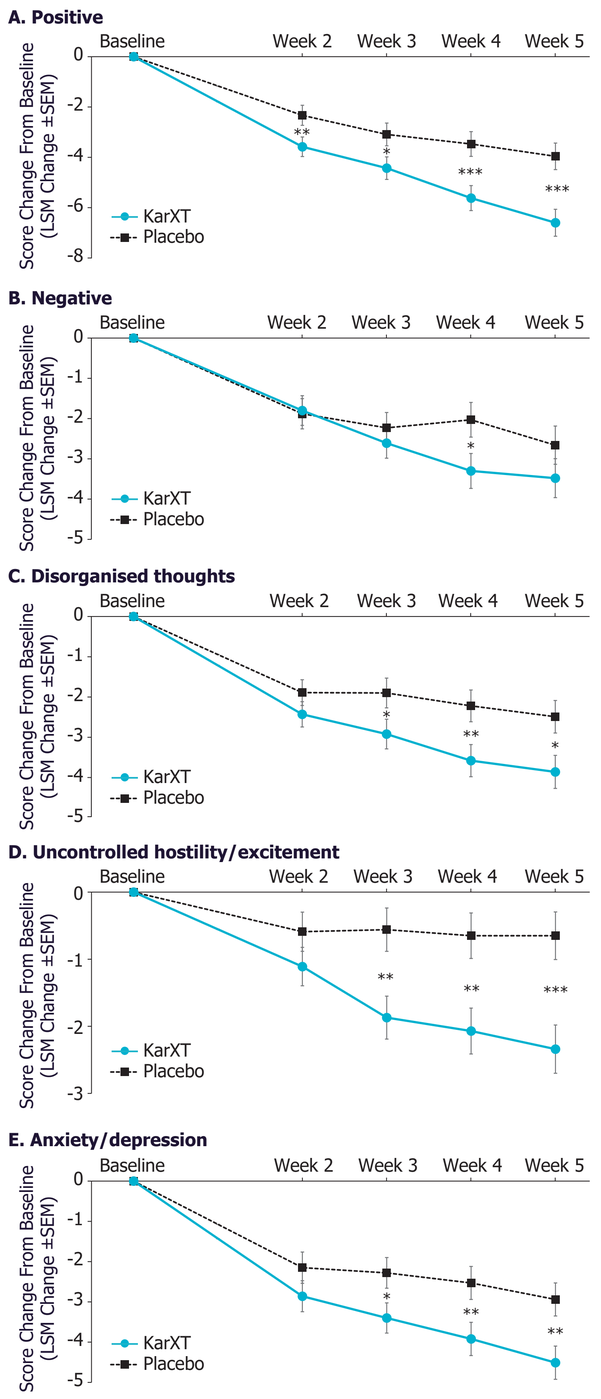
[a]Represents within-group difference from baseline to week 5. [b]Positive factor includes 8 items; score range, 8-56. [c]Negative factor includes 7 items; score range, 7-49. [d]Disorganised thoughts factor includes 7 items; score range, 7-49. [e]Uncontrolled hostility/excitement factor includes 4 items; score range, 4-28. [f]Anxiety/depression factor includes 4 items; score range, 4-28.
LSM, least squares mean; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Figure 2. PANSS Categorical Response by Trial Week



PANSS, Positive and Negative Syndrome Scale.

Figure 3. Effect of KarXT on PANSS Marder Factor Domains of Response



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

Conclusions

- In EMERGENT-3, KarXT was associated with higher response rates for clinically meaningful PANSS total score improvement thresholds vs placebo in people with schizophrenia experiencing acute psychosis
- In addition, KarXT was associated with significant improvements vs placebo at week 5 in PANSS Marder positive, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression factors, suggesting that KarXT was associated with a broad range of symptom improvements
- If approved, KarXT has the potential to be the first in a new class of treatments for people with schizophrenia based on muscarinic receptor agonism and an alternative to D_2 dopamine receptor antagonists

References

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