The Potential Role of the M_1/M_4 Muscarinic Receptor Agonist KarXT in the Treatment of Cognitive Impairment in Patients With Schizophrenia

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Introduction

- Schizophrenia is characterised by broad cognitive impairment across multiple domains (eg, executive function, attention, memory, processing speed), which often precedes the onset of psychosis[1]
- Although not all people with schizophrenia perform in the impaired range on cognitive test batteries, cognitive impairment is robustly associated with worse functioning across multiple domains, including independent living, work, and social connections
- Despite major functional consequences, there are currently no pharmacologic treatments available for cognitive impairment associated with schizophrenia[2]
- KarXT (xanomeline–trospium chloride) is being investigated as a possible treatment for both psychosis and cognitive impairment in people with schizophrenia[3-5]
- KarXT's therapeutic effects are believed to be mediated through direct agonism of M_1 and M_4 muscarinic receptors,[6] unlike all currently approved antipsychotic medications for schizophrenia, which directly bind D_2 dopamine receptors
- The central muscarinic acetylcholine system plays a key role in cognition and has been the target of numerous drug development efforts for cognitive impairment[7-10]
  - Converging lines of preclinical and human evidence suggest that M_1 and M_4 muscarinic receptors may be important therapeutic targets for treatment of both cognitive impairment and psychosis
  - Furthermore, xanomeline has been shown to improve cognition in Alzheimer's disease[11] and in a proof-of-concept trial in schizophrenia[12]
- In the previous EMERGENT-1 trial (NCT03697252), KarXT was associated with robust improvements in Positive and Negative Syndrome Scale (PANSS) total scores (primary endpoint) and in positive and negative symptoms (secondary outcome measures).[3] On an exploratory cognitive outcome measure, cognitive improvement was numerically but not statistically greater with KarXT than placebo. However, post hoc analysis of participants who demonstrated clinically significant cognitive impairment at baseline indicated that those treated with KarXT showed cognitive improvement compared with those on placebo[13]
- Topline results for the phase 3 EMERGENT-2 (NCT04659161)[4] and EMERGENT-3 (NCT04738123)[5] trials also indicated that KarXT demonstrated robust improvement in PANSS total score. Here we report analysis of the exploratory congition outcome measure from the phase 3 EMERGENT-2 and EMERGENT-3 trials and provide a comparison with the EMERGENT-1 results

Objective

- Evaluate the impact of KarXT on cognitive performance in the combined sample of participants from EMERGENT-2 and EMERGENT-3

Methods

- EMERGENT-2 and EMERGENT-3 used the same trial design and were highly similar to EMERGENT-1. All trials were 5-week, randomised, double-blind, placebo-controlled, inpatient trials of KarXT in people with schizophrenia experiencing acute psychosis
  - Participants were randomised 1:1 to receive oral KarXT or matched placebo twice daily (BID) for 5 weeks
  - KarXT (mg xanomeline/mg trospium) was dosed flexibly, starting with 50 mg/20 mg BID and increasing to a maximum of 125 mg/30 mg BID

Cognitive Assessments

- For EMERGENT-2 and EMERGENT-3, cognition was assessed using a standardised composite score from the Cambridge Neuropsychological Test Automated Battery (CANTAB) at 3 time points: baseline, week 3, and week 5
  - Domains assessed: attention (Rapid Visual Information Processing Test), verbal memory (Verbal Recognition Memory Test–Free Recall), visual working memory (Spatial Span Test), executive function (One Touch Stockings of Cambridge Test)
  - Analyses used a predefined composite score comprising 1 index from each of the 4 domains
  - Participants were identified as "impaired" based on performing ≥1 standard deviation below normative standards at baseline
- For EMERGENT-1, cognition was assessed using a standardised composite score from the Cogstate battery at 2 time points: baseline and week 5
  - Domains assessed: attention (Identification Test), processing speed (Detection Test), executive function (Groton Maze Learning Test), working memory (One Back Test), verbal learning (International Shopping List Test)

Analyses

- Analyses were performed in the modified intent-to-treat population, defined as all randomised participants who received ≥1 dose of trial medication, had a baseline CANTAB assessment, and had ≥1 postbaseline CANTAB assessment
- In the combined sample of participants from EMERGENT-2 and EMERGENT-3, we report baseline characteristics for the full sample
- For the full sample and for the impaired subsample, CANTAB composite score change from baseline to week 5 was compared for KarXT vs placebo using mixed models for repeated measures with treatment group, visit, and their interaction as fixed factors and baseline score, age, sex, and trial as covariates
- The relationship between change in cognitive performance and change in PANSS total score was evaluated within the KarXT and placebo groups using partial correlations adjusted for the effect of sex, age, baseline cognition, baseline PANSS score, and trial as covariates

Results

EMERGENT-2/EMERGENT-3 Results

- Baseline characteristics were similar between the KarXT and placebo groups in the combined EMERGENT-2/EMERGENT-3 sample, with no significant differences between groups in demographics or PANSS scores (**Table 1**)
- In the full sample, the difference in CANTAB composite score change from baseline to week 5 between KarXT and placebo was not statistically significant (**Table 2**; LSM difference=0.06; SE=0.06; *P*=0.33)
- Within the cognitively impaired subgroup, KarXT was associated with significant improvement from baseline to week 5 in CANTAB composite score compared with placebo (**Table 2**; **Figure 1**; LSM difference=0.29; SE=0.10; *P*<0.01). The score change difference favoring KarXT at week 3 was not statistically significant (LSM difference=0.13; SE=0.09; *P*=0.12)
- There was no significant relationship between changes in PANSS total score and changes in CANTAB composite score in those taking KarXT (partial *r*=0.04; *P*=0.66; **Figure 2**) or placebo (partial *r*=-0.13; *P*=0.12). This suggests that pseudospecific improvements in cognition as a result of overall PANSS-related symptoms improvement were minimal

EMERGENT-1 Comparison

- The results from EMERGENT-2/EMERGENT-3 are similar to EMERGENT-1 (**Table 3**), with:
  - A significant improvement in the subgroup with cognitive impairment at baseline
  - A nonsignificant trend toward greater improvement with KarXT vs placebo observed in the entire sample

Table 1. EMERGENT-2/EMERGENT-3 Baseline Characteristics (mITT Population)

Variable	KarXT (n=152)	Placebo (n=160)	Overall (N=312)
Trial, n (%)			
EMERGENT-2	74 (48.7)	71 (44.4)	145 (46.5)
EMERGENT-3	78 (51.3)	89 (55.6)	167 (53.5)
Age, mean±SD	44.8±10.71	44.2±11.55	44.5±11.14
Sex, n (%)			
Female	41 (27.0)	31 (19.4)	72 (23.1)
Male	111 (73.0)	129 (80.6)	240 (76.9)
Race, n (%)			
Asian	2 (1.3)	0	2 (0.6)
Black or African American	109 (71.7)	106 (66.3)	215 (68.9)
White	41 (27.0)	54 (33.8)	95 (30.5)
Cognitive impairment, n (%)			
Impaired	69 (45.4)	65 (40.6)	134 (43.0)
Not impaired	83 (54.6)	95 (59.4)	178 (57.0)
Baseline PANSS total score, mean±SD	97.7±8.94	96.5±8.88	97.1±8.91
Baseline PANSS positive subscale score, mean±SD	27.0±3.73	26.2±3.39	26.6±3.58
Baseline PANSS negative subscale score, mean±SD	22.4±3.61	22.4±3.73	22.4±3.66
Baseline CANTAB composite score, mean±SD	0.1±0.67	0.1±0.63	0.1±0.65

CANTAB, Cambridge Neuropsychological Test Automated Battery; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Table 2. EMERGENT-2/EMERGENT-3 KarXT Treatment Effect on Cognitive Impairment

Sample	Treatment	LSM Change From Baseline ±SE at Week 5	KarXT vs Placebo		
			LSM Difference ±SE	*P* value	Cohen's *d*
Full sample	KarXT (n=152)	0.13±0.05	0.06±0.06	0.33	0.12
	Placebo (n=160)	0.07±0.05			
Impaired	KarXT (n=69)	0.41±0.07	0.29±0.10	<0.01	0.52
	Placebo (n=65)	0.13±0.08			

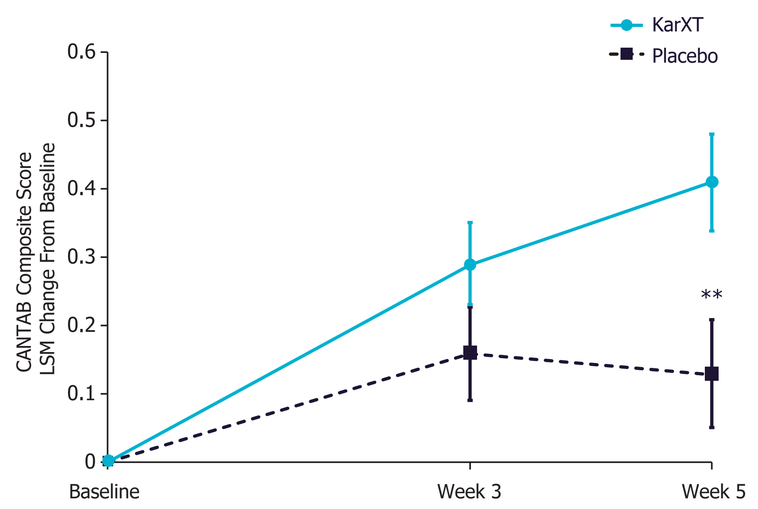
LSM, least squares mean; SE, standard error.

Table 3. EMERGENT-1 KarXT Treatment Effect on Cognitive Impairment

Sample	Treatment	LSM Change From Baseline ±SE at Week 5	KarXT vs Placebo		
			LSM Difference ±SE	*P* value	Cohen's *d*
Full sample	KarXT (n=60)	0.13±0.11	0.18±0.13	0.16	0.20
	Placebo (n=65)	-0.05±0.11			
Impaired	KarXT (n=23)	0.57±0.19	0.50±0.22	0.03	0.50
	Placebo (n=37)	0.07±0.13			

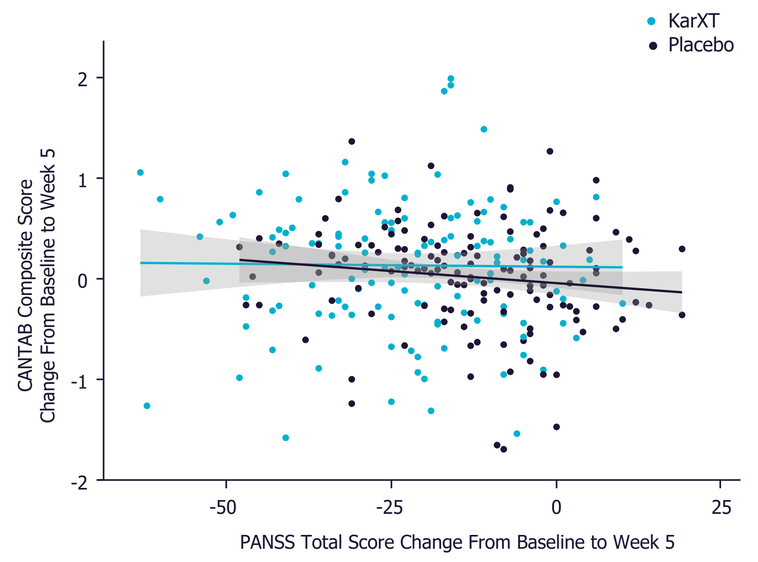
LSM, least squares mean; SE, standard error.

Figure 1. EMERGENT-2/EMERGENT-3 Change in CANTAB Composite Score Over Time Within the Cognitively Impaired Subsample



**P<0.01.
Values are ±standard error. CANTAB, Cambridge Neuropsychological Test Automated Battery; LSM, least squares mean.

Figure 2. EMERGENT-2/EMERGENT-3 Relationship Between Changes in CANTAB Composite Score and PANSS Total Score



CANTAB, Cambridge Neuropsychological Test Automated Battery; PANSS, Positive and Negative Syndrome Scale.

Summary

- KarXT was associated with improved cognitive function in the combined groups who entered EMERGENT-2/EMERGENT-3 with cognitive impairment at baseline, as defined by being ≥1 standard deviation below population norms
- Consistent with results from EMERGENT-1, the magnitude of improvement for KarXT vs placebo within the cognitively impaired subsample had a medium effect size (Cohen's *d*=0.52) in the combined EMERGENT-2/EMERGENT-3 analyses, which included a larger number of participants, a different cognitive battery, and an additional interim cognitive assessment that permitted a more robust data analytic approach
- Across the EMERGENT trials, we have observed nominal, nonsignificant increases in cognitive performance for KarXT in the full, unstratified samples with no evidence of clinically meaningful worsening of cognitive performance
- Similar to findings from EMERGENT-1, results here reveal that the impact of KarXT on cognitive performance (measured by CANTAB) and positive and negative symptoms of schizophrenia (measured by the PANSS total score) were largely independent, suggesting that improvements in cognitive performance observed in these analyses are not attributable to improvement in clinical symptoms
- These results further demonstrate the potential of KarXT, a dual M_1/M_4 muscarinic receptor agonist, as a potential procognitive treatment when combined with the results from 3 previous placebo-controlled clinical trials in people with schizophrenia and Alzheimer's disease, numerous preclinical studies, and the understanding of the role for the muscarinic acetylcholine system in cognitive function
- To follow up on these initial analyses, we will thoroughly evaluate the rich set of performance indices from CANTAB to determine if the prespecified composite score indices are optimally suited to detect treatment-related changes. As in the EMERGENT-1 cognition data analyses, we will also examine intraindividual variability in performance across the cognitive subtests at each visit to identify potential sources of data variability
- These exploratory analyses of 5-week trials in acutely symptomatic inpatients with schizophrenia must be interpreted with caution, and further investigation in clinically stable outpatients is warranted to characterise the effects of KarXT on cognitive impairment associated with schizophrenia

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Disclosures

CS, SEY, ACM, SKB, ISR, WPH, and SMP are employees of and hold equity in Karuna Therapeutics. PDH is a consultant for Alkermes, Boehringer-Ingelheim, BioExcel, Karuna Therapeutics, Merck, Minerva Pharmaceuticals, SK Pharma, and Sunovion/DSP and has received royalties from VeraSci. EW and FC provide consulting services for Karuna Therapeutics.

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