KarXT Treatment Improves Cognitive Performance in Cognitively Impaired Patients with Schizophrenia: A *Post hoc* Analysis of the Phase 2 EMERGENT-1 Study

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BACKGROUND

Cognitive impairment is a core symptom of schizophrenia, associated with reduced overall functioning and quality of life, for which currently available treatments (antipsychotics) show little therapeutic benefit.[1] KarXT, an investigational muscarinic agonist, may hold promise as a potential treatment for psychosis and cognitive impairment through its activity at M_4 and M_1, respectively.[2] The Phase 2 EMERGENT-1 study (NCT03697252) showed that, in addition to robustly improving positive and negative symptoms of schizophrenia,[3] treatment with KarXT was associated with a trend toward greater cognitive improvement compared to placebo. However, a substantial proportion of participants in this study had minimal to no cognitive impairment at study baseline. Previous studies have established that as many as one in three patients with schizophrenia may score within the cognitively normal range, and that these individuals have fewer cognitively mediated functional impairments and may be less responsive to treatment.[4-6] In this *post hoc* analysis, we assess the impact of KarXT on cognitive performance in study participants with and without significant cognitive impairment at study baseline.

RESULTS

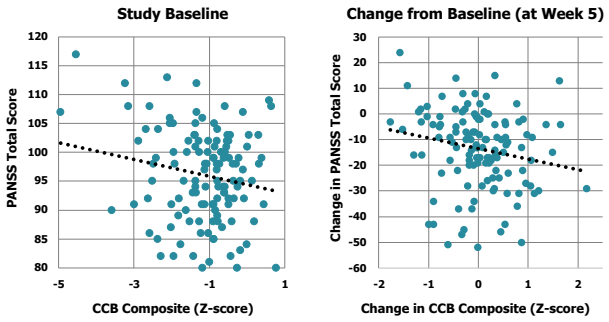
Table 1. Baseline Characteristics by Impairment Subgroup

	Evaluable Population		Minimally Impaired		Impaired	
	KarXT N = 60	Placebo N = 65	KarXT N = 37	Placebo N = 28	KarXT N = 23	Placebo N = 37
Age	45.0 (10.3)	42.5 (9.8)	45.0 (10.8)	42.3 (9.8)	44.9 (9.6)	42.7 (10.0)
Gender, n male (%)	48 (80%)	45 (69.2%)	28 (78.4%)	22 (78.6%)	19 (82.6%)	23 (62.2%)
PANSS Total	96.4 (8.8)	95.7 (7.3)	95.9 (7.9)	94.5 (6.1)	97.3 (10.2)	96.7 (8.0)
PANSS Negative	22.7 (4.4)	22.5 (4.2)	22.1 (3.1)	22.3 (4.8)	23.6 (5.9)	22.7 (3.7)
PANSS Positive	25.8 (3.3)	26.1 (3.5)	26.0 (3.0)	25.6 (3.7)	25.7 (3.9)	26.4 (3.3)
CCB Composite (Z-score)	-1.00 (1.00)	-1.25 (0.96)	-0.41 (0.49)	-0.45 (0.36)	-1.95 (0.86)	-1.86 (0.81)
Identification	-0.68 (1.55)	-1.57 (1.57)	-0.04 (1.28)	-0.35 (1.07)	-1.71 (1.41)	-2.49 (1.24)
Detection	-0.55 (1.59)	-1.26 (1.45)	0.03 (1.27)	-0.48 (1.29)	-1.47 (1.65)	-1.84 (1.30)
Groton Maze Learning	-1.52 (1.96)	-1.66 (2.58)	-0.86 (1.40)	-0.64 (1.23)	-2.58 (2.27)	-2.43 (3.05)
One-Back	-1.22 (1.63)	-0.85 (1.48)	-0.44 (1.10)	-0.21 (1.23)	-2.48 (1.57)	-1.34 (1.48)
Int'l Shopping List	-1.03 (0.95)	-0.93 (0.91)	-0.72 (0.91)	-0.55 (0.84)	-1.53 (0.80)	-1.22 (0.86)

Note: All values reflect group means and (standard deviation) unless otherwise indicated.
CCB = Cogstate computerized cognitive battery. CCB values reflect z-scores.

Study participants were separated into two subgroups based on their Cogstate computerized cognitive battery (CCB) composite scores at baseline: "minimally impaired," defined as those performing within 1 SD of the normative mean, and "impaired," those who scored more than 1 SD below the normative mean. Baseline characteristics were similar across impairment groups, with no significant differences in demographics or PANSS scores observed (p-values > 0.14).

Figure 1. Relationship Between CCB Composite Score and PANSS Total at Baseline and After 5-weeks of Treatment



In the mITT completer sample (N = 125), there was a small significant relationship between PANSS total score and CCB score at baseline (β = -0.19, p=0.03, adjusted R2 = 0.07), and between the change from baseline to week 5 CCB and PANSS total scores (β = -0.20, p = 0.03, adjusted R2 = 0.03).

		LS Means CFB at Day 35	95% Confidence Interval		Model Results		
Sample	**Treatment**	**Estimate (SE)**	**Lower**	**Upper**	**t-value**	**p-value**	**Cohen's d**
mITT Completers	KarXT (N = 60)	0.13 (0.11)	-0.10	0.35	1.13	0.26	0.15
	Placebo (N = 65)	-0.05 (0.11)	-0.27	0.17	-0.48	0.63	0.06
	KarXT vs Placebo	0.18 (0.13)	-0.44	0.08	1.40	0.16	0.20
Minimally Impaired	KarXT (N = 37)	-0.18 (0.13)	-0.44	0.09	-1.33	0.19	0.22
	Placebo (N = 28)	-0.22 (0.15)	-0.52	0.08	-1.47	0.15	0.28
	KarXT vs Placebo	0.04 (0.16)	-0.28	0.37	0.26	0.79	0.05
Impaired	KarXT (N = 23)	0.57 (0.19)	0.18	0.95	**2.93**	**0.01**	**0.61**
	Placebo (N = 37)	0.07 (0.13)	-0.19	0.33	0.55	0.59	0.09
	KarXT vs Placebo	0.50 (0.22)	0.04	0.95	**2.19**	**0.03**	**0.50**

Table 2. KarXT Treatment Effect on Cognitive Performance by Baseline Impairment Subgroup

In the "minimally impaired" subgroup, there was no significant difference in cognitive performance between KarXT and placebo after 5-weeks of treatment. In contrast, in the "impaired" subgroup KarXT was associated with meaningful and significant improvements in cognitive performance, whereas there was no meaningful change in cognitive performance in the placebo arm.

METHODS

An abbreviated version of the Cogstate computerized cognitive battery (CCB) was administered as an exploratory endpoint in EMERGENT-1, a Phase 2 randomized, double-blind, placebo-controlled, 5-week inpatient trial in adults (N = 182) with acute exacerbation(s) of schizophrenia. 138 study participants completed the trial and provided valid PANSS scores at all timepoints. Of the 138 participants included for analysis, 13 had missing cognitive data on at least one subtest of the CCB (3 at baseline and 10 at week 5). The mITT completers sample (N = 125), including participants who had valid CCB and PANSS scores at baseline and end of study, were separated into two groups based on cognitive impairment at study baseline using a cutoff score of -1 SD relative to the normative sample mean. This cutoff was selected based on its previous use to differentiate cognitively impaired and non-impaired patients with schizophrenia, and because it has been shown to best differentiate clinically impaired and unimpaired populations in clinical neuropsychological testing.[5-7] Separate ANCOVA models assessed treatment effects in each subgroup, with covariates of age, sex, site and baseline CCB composite score. Potential relationships between cognitive performance and PANSS scores were assessed using linear regression and using the same covariates.

CONCLUSIONS

- These results suggest that KarXT may significantly improve cognitive performance in patients with schizophrenia who exhibit cognitive impairment prior to treatment.
- In this study over half of the study participants in the evaluable sample were performing within 1 SD of the normative mean at baseline and did not benefit from treatment with KarXT. This finding is consistent with the literature, which suggests that drugs such as acetylcholinesterase inhibitors that are effective in those exhibiting cognitive decline or impairment may be less beneficial in those without cognitive impairment.[8]
- As a result of the study design and analytic approach, it is impossible to fully address questions of pseudospecificity and the impact of regression to the mean on the results. However, correlations were modest, with only 3% of the variance in cognitive improvement accounted for by change in PANSS total score. Potential regression to the mean was only seen in the "minimally impaired" subgroup.
- While promising, these results must be replicated in future studies that are specifically designed to assess the effects of KarXT on cognitive performance.
- Consistent with trial designs in studies of positive and negative symptoms of schizophrenia, future studies of cognition should consider including a minimal cognitive impairment eligibility criterion. Additionally, in acute psychosis trials that include cognitive endpoints, prespecifying a subgroup analysis based on cognitive impairment at baseline may be a valuable approach.

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