Potential Impact of KarXT on Negative Symptoms in Acute Schizophrenia: An Analysis of Pooled Data From 3 Trials

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Introduction

- Currently approved antipsychotic medications do not adequately treat negative symptoms of schizophrenia, a major driver of functional disability
- More efficacious treatments based on new mechanistic targets are needed, particularly medications with broader efficacy across multiple symptom domains
- KarXT (xanomeline–trospium chloride) is a potential new treatment for people with schizophrenia with a novel mechanism of action based on M_1/M_4 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 positive and negative 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
- Here, we use post hoc analyses of pooled data from the EMERGENT trials to examine the possibility that KarXT has a direct treatment benefit for negative symptoms of schizophrenia that is independent and not secondary to improvements in positive or other symptoms

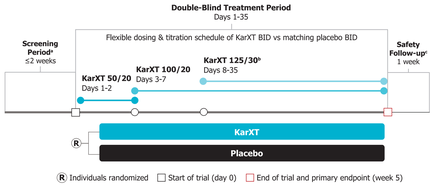
Objectives

- To evaluate the effect of KarXT on negative symptoms of schizophrenia in a subgroup of people with moderate/severe negative symptoms and no predominance of positive symptoms
- To assess the effect of KarXT on the PANSS negative symptom domains of diminished emotional experience and expression

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

Figure 1. 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. [c]EMERGENT-2 and EMERGENT-3 only.
BID, twice daily.

- 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 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 1 baseline and ≥1 postbaseline PANSS assessment
- A subgroup of participants with prominent negative symptoms was identified using the following previously published criteria[4]
  - PANSS Marder negative factor score ≥24, which consists of blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity (N6), motor retardation (G7), and active social avoidance (G16)[5];
  - PANSS Mohr positive score ≤19, which consists of delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6), and unusual thought content (G9)[6]; and
  - Scores ≥4 on at least 2 of 3 PANSS blunted affect, passive/apathetic social withdrawal, or lack of spontaneity/flow of conversation items[7]
- Mixed model for repeated measures (MMRM) analyses were used to evaluate change from baseline to week 5 in PANSS Marder negative factor score in the full sample and the subgroup of participants with prominent negative symptoms
- Positive symptoms, depression, depression/anxiety, disorganized thoughts, and hostility were included as covariates in MMRM analyses to assess whether changes in negative symptoms were independent of changes in other symptoms
- MMRM analyses were used to explore the effect of KarXT on 2 PANSS negative symptom subdomains
  - Reduced emotional experience: emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and active social avoidance (G16)
  - Reduced emotional expression: blunted affect (N1), poor rapport (N3), lack of spontaneity (N6), and motor retardation (G7)

Results

Participants

- A total of 640 participants (KarXT, n=314; placebo, n=326) were included in the mITT population used for pooled efficacy analyses
- Baseline demographics and characteristics in the full sample and the subgroup with prominent negative symptoms are summarized in **Table 1**

Table 1. Baseline Demographics and Characteristics (mITT Population)

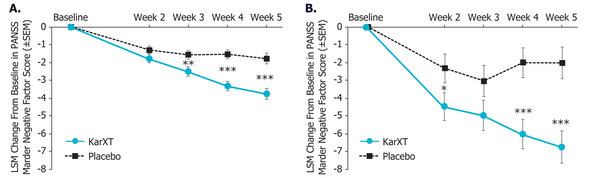
Parameter	Full Sample		Prominent Negative Symptom Subgroup	
	KarXT (n=314)	Placebo (n=326)	KarXT (n=29)	Placebo (n=35)
Age, years, mean±SD	44.6±10.66	43.7±11.33	46.7±10.46	44.7±11.16
Sex, n (%)				
Male	233 (74.2)	250 (76.7)	23 (79.3)	32 (91.4)
Female	81 (25.8)	76 (23.3)	6 (20.7)	3 (8.6)
Race, n (%)				
Asian	4 (1.3)	2 (0.6)	0	1 (2.9)
Black	225 (71.7)	221 (67.8)	25 (86.2)	26 (74.3)
Native Hawaiian or other Pacific Islander	1 (0.3)	1 (0.3)	0	0
White	83 (26.4)	98 (30.1)	4 (13.8)	8 (22.9)
Other	1 (0.3)	4 (1.2)	0	0
Ethnicity, n (%)				
Hispanic or Latino	47 (15.0)	34 (10.4)	2 (6.9)	2 (5.7)
Not Hispanic or Latino	265 (84.4)	291 (89.3)	27 (93.1)	33 (94.3)
Not reported	2 (0.6)	1 (0.3)	0	0
Country, n (%)				
United States	295 (93.9)	300 (92.0)	27 (93.1)	32 (91.4)
Ukraine	19 (6.1)	26 (8.0)	2 (6.9)	3 (8.6)
PANSS Marder factor scores, mean±SD				
Negative	22.4±4.51	22.3±4.62	27.6±3.11	26.6±2.13
Positive	30.8±3.88	30.6±3.74	26.3±1.98	26.6±2.23
Disorganization	22.0±3.81	21.9±3.92	21.4±4.12	22.5±3.90
Depression/anxiety	12.4±3.23	12.4±3.22	11.8±2.83	10.5±3.17
Excitability/hostility	10.0±3.19	9.9±3.00	10.1±3.14	8.1±3.30
PANSS reduced emotional experience, mean±SD	11.7±2.08	11.5±2.11	12.8±1.54	11.9±1.94
PANSS reduced emotional expression, mean±SD	10.7±3.47	10.8±3.58	14.8±2.52	14.6±1.91
PANSS Mohr positive, mean±SD	21.7±2.93	21.6±2.79	17.9±1.03	18.1±0.91

mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Effect of KarXT on Negative Symptoms in the Full Sample and Subgroup With Prominent Negative Symptoms

- In the full sample, KarXT (n=314) was associated with a significantly greater improvement from baseline to week 5 in PANSS Marder negative factor score compared with placebo (n=326) (least squares mean [LSM] difference=-1.97, standard error [SE]=0.40, P<0.0001; Cohen's d=0.42; **Figure 2A**)
- A total of 64 participants (10%) met criteria for having prominent negative symptoms at baseline. In this subgroup, KarXT (n=29) was associated with a significantly greater reduction from baseline to week 5 in PANSS Marder negative factor score compared with placebo (n=35) (LSM difference=-4.71, SE=1.16, P<0.0001; Cohen's d=1.18) (**Figure 2B**)

Figure 2. Change in PANSS Marder Negative Factor Score in the (A) Full Population and (B) Subgroup With Prominent Negative Symptoms



*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.

- The effect of KarXT on change from baseline to week 5 in PANSS Marder negative factor score in the subgroup with prominent negative symptoms remained significantly greater than in the placebo group after covarying for positive symptoms, depression/anxiety, disorganized thoughts, or hostility (**Table 2**)

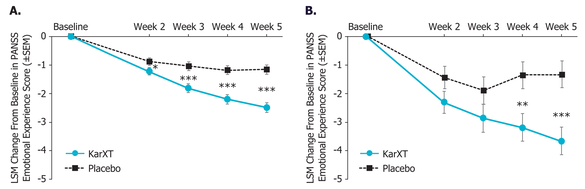
Table 2. Change in PANSS Marder Negative Factor Score Over 5 Weeks in Participants With Prominent Negative Symptoms

Covariate	Participants With Prominent Negative Symptoms			
	KarXT–Placebo LSM Difference at Week 5	Standard Error	*P* Value	Cohen's *d*
PANSS Marder positive factor	-3.28	1.07	<0.01	0.94
PANSS Marder depression/anxiety factor	-4.68	1.18	<0.001	1.17
PANSS Marder disorganized thoughts factor	-3.07	0.96	<0.01	0.96
PANSS Marder hostility factor	-3.74	1.16	<0.01	0.98

LSM, least squares mean; PANSS, Positive and Negative Syndrome Scale.

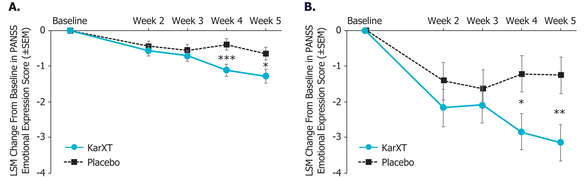
- In both the full population and the subgroup with prominent negative symptoms, KarXT was associated with significantly greater improvements from baseline to week 5 in both diminished emotional experience (Cohen's d=0.52 vs 1.08; **Figure 3**) and emotional expression (Cohen's d=0.22 vs 0.84; **Figure 4**)

Figure 3. Change in PANSS Diminished Emotional Experience in the (A) Full Population and (B) Subgroup With Prominent Negative Symptoms



*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.

Figure 4. Change in PANSS Diminished Emotional Expression in the (A) Full Population and (B) Subgroup With Prominent Negative Symptoms



*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 these post hoc pooled analyses from 3 EMERGENT trials, KarXT was associated with significant improvement in negative symptoms compared with placebo in both the full sample and the subgroup of participants with prominent negative symptoms
- In the subgroup with prominent negative symptoms, the effect of KarXT on negative symptoms remained significant after covarying for all types of symptoms, suggesting this treatment effect was not secondary to improvement in other symptoms
- KarXT was also associated with significant improvement in diminished emotional experience and emotional expression in the full sample and the subgroup with prominent negative symptoms
- Collectively, these findings are consistent with the possibility that KarXT could be a broad-spectrum monotherapy and directly improve negative symptoms in people with schizophrenia experiencing acute psychosis
  - Our findings are supported by preclinical evidence that muscarinic receptor (particularly M_1) agonists improve deficits in animal models of negative symptoms[8]
- The results from these exploratory analyses must be interpreted with caution; further investigation of the effects of KarXT on negative symptoms in a larger sample of stable outpatients with predominant negative symptoms is warranted

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Disclosures

WPH, AC, IK, SS, ACM, SMP, and SKB are employees of and hold equity in Karuna Therapeutics. SDT is an employee of Signant Health and a consultant to Karuna Therapeutics.

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