Pooled Analysis of EPS-Like Symptoms in the EMERGENT Program of KarXT in Schizophrenia

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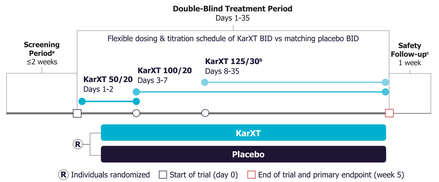
Introduction

- All current antipsychotics approved for the treatment of schizophrenia have direct affinity for D_2 dopamine receptors and therefore are associated with known safety and tolerability problems associated with dopamine receptor antagonism, notably drug-induced movement disorders.[1] Often referred to as extrapyramidal symptoms (EPS), these movement disorders include akathisia, acute dystonia, parkinsonian tremor and rigidity, and dyskinetic movements
- Newer medications have reduced but not eliminated the overall burden of EPS, which remains a clinical problem.[1] There continues to be a high unmet need for effective antipsychotics without EPS/motor side effects
- KarXT (xanomeline–trospium chloride), an investigational medication, contains a muscarinic agonist, xanomeline, which preferentially targets the M_1 and M_4 muscarinic receptor subtypes.[2,3] Xanomeline has no direct affinity for any dopamine receptor and does not induce EPS-like movements in animal models (eg, no catalepsy), providing a clear rationale that xanomeline may not be associated with EPS
- KarXT was developed with the intention of preserving the desired therapeutic benefit of xanomeline's activation of M_1 and M_4 muscarinic receptors in the central nervous system while simultaneously reducing the risk for undesired side effects. Thus, coupling xanomeline with the peripheral muscarinic receptor–blocking anticholinergic, trospium chloride, may reduce many of these common side effects[2,3]
- KarXT is being investigated as a potential treatment for adults with schizophrenia and is currently in late phase 3 development. The efficacy, safety, and tolerability of KarXT were evaluated in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252),[4] EMERGENT-2 (NCT04659161),[5] and EMERGENT-3 (NCT04738123)[6] trials (**Figure 1**)
- In the EMERGENT trials,[4-6] KarXT significantly improved symptoms of schizophrenia compared with placebo as measured by change from baseline to week 5 in Positive and Negative Syndrome Scale (PANSS) total score and was generally well tolerated
- This pooled analysis of safety data from three 5-week EMERGENT trials investigated the occurrence of EPS adverse events in people with schizophrenia treated with KarXT compared with placebo

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.

Objective

- To characterize rates of new-onset EPS associated with KarXT vs placebo in people with schizophrenia experiencing acute psychosis using pooled data from the EMERGENT trials

Methods

- EMERGENT-1 and EMERGENT-2 enrolled participants from the United States and EMERGENT-3 enrolled participants from the United States and Ukraine
- 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
- Eligible participants were required to have a PANSS total score ≥80 and Clinical Global Impression–Severity score ≥4
- Eligible participants were randomized 1:1 to receive oral KarXT or matched placebo twice daily (BID) for 5 weeks (**Figure 1**)
  - 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
- All safety analyses were conducted in the safety population, defined as all randomized participants who received ≥1 dose of trial medication (KarXT or placebo)
- Treatment-emergent adverse events (TEAEs) were assessed by the investigator to determine relatedness to trial medication; TEAEs deemed as "possibly," "probably," or "definitely" related to trial medication, as well as those with unknown relationship, were categorized as "treatment related"
- Here, EPS were broadly defined as any TEAE (any new-onset adverse event [AE] occurring after the first dose of trial medication) with a preferred term of dystonia, dyskinesia, akathisia, or extrapyramidal disorder
- In addition to TEAE reporting, EPS, as defined in these trials, were evaluated using the following assessments
  - Simpson-Angus Scale (SAS): 10-item scale used to rate EPS, including hypokinesia, rigidity, glabellar tap, tremor, and salivation. Items are rated on a 5-point scale with a total score obtained by summing items and dividing by 10
  - Barnes Akathisia Rating Scale (BARS): 4-item scale rating trial participants based on clinician observation, self-report of restlessness, and self-reported distress related to restlessness. Together, these items produce a global clinical assessment of akathisia
  - Abnormal Involuntary Movement Scale (AIMS): 12-item scale rating involuntary movements across areas of the body. Items are rated on a 5-point scale of severity from 0 to 4. A total score on the AIMS reflects presence and severity of potential tardive dyskinesia

Results

Participants

- A total of 683 participants (KarXT, n=340; placebo, n=343) were included in the safety population used for the pooled safety analyses
- There were no meaningful differences in demographic characteristics between treatment groups at baseline (**Table 1**)

Table 1. Baseline Demographics and Characteristics Pooled Across EMERGENT-1, EMERGENT-2, and EMERGENT-3 (Safety Population)

Parameter	KarXT (n=340)	Placebo (n=343)
Age (years), mean±SD	44.3±10.8	43.7±11.3
Sex, n (%)		
Male	254 (74.7)	262 (76.4)
Female	86 (25.3)	81 (23.6)
Race, n (%)		
Asian	4 (1.2)	3 (0.9)
Black	242 (71.2)	235 (68.5)
Native Hawaiian or other Pacific Islander	1 (0.3)	1 (0.3)
White	92 (27.1)	99 (28.9)
Other	1 (0.3)	4 (1.2)
Not reported	0	1 (0.3)
Ethnicity, n (%)		
Hispanic or Latino	50 (14.7)	37 (10.8)
Not Hispanic or Latino	288 (84.7)	305 (88.9)
Not reported	2 (0.6)	1 (0.3)
Country, n (%)		
United States	319 (93.8)	316 (92.1)
Ukraine	21 (6.2)	27 (7.9)
Weight (kg), mean±SD	88.6±18.7	87.2±18.4
BMI (kg/m^2), mean±SD	29.1±5.5	28.9±5.3

BMI, body mass index; SD, standard deviation.

Rates of Movement Disorder Treatment-Emergent Adverse Events (TEAEs)

- The overall rate of EPS TEAEs was 3.2% in the KarXT group vs 0.9% in the placebo group
  - The most commonly reported EPS TEAE was akathisia (KarXT, 2.4%; placebo, 0.9%)
- EPS TEAEs deemed to be related to trial medication were reported by 1.5% of participants in the KarXT group vs 0.3% in the placebo group (**Table 2**)
- Most EPS TEAEs with KarXT were reported as mild in intensity, resolved with continued treatment, and were not accompanied by changes in EPS scales compared with placebo
- Dystonia, dyskinesia, and extrapyramidal disorder TEAEs were each reported by 1 participant (0.3%) in the KarXT arm, all of which were considered by the investigator to be related to treatment
- There were no TEAE reports of tardive dyskinesia

Table 2. EPS TEAEs Related to Trial Medication

Parameter	KarXT (n=340)	Placebo (n=343)
Any related EPS TEAE,[a] n (%)	5 (1.5)	1 (0.3)
Akathisia	2 (0.6)	1 (0.3)
Dyskinesia	1 (0.3)	0
Dystonia	1 (0.3)	0
Extrapyramidal disorder	1 (0.3)	0

[a]Related EPS TEAEs included any new onset of dystonia, dyskinesia, akathisia, or extrapyramidal disorder reported at any time after the first dose of trial medication and that was deemed related to trial medication by the investigator.
EPS, extrapyramidal symptoms; TEAE, treatment-emergent adverse event.

Change in Movement Disorder Scale Scores

- KarXT was associated with no clinically meaningful changes from baseline to week 5 in SAS, BARS, or AIMS scores compared with placebo (**Table 3**)

Table 3. Mean Change in Movement Disorder Scale Scores During the 5-Week Treatment Period (Safety Population)

Parameter	KarXT (n=340)	Placebo (n=343)
SAS total score mean change from baseline to week 5 ±SD	-0.1±0.62	-0.1±0.63
BARS total score mean change from baseline to week 5 ±SD	-0.1±0.90	-0.1±0.84
AIMS total score of items 1-7 mean change from baseline to week 5 ±SD	0.0±0.66	0.0±0.15

AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; SAS, Simpson-Angus Scale; SD, standard deviation.

Conclusions

- In the pooled analysis of placebo-controlled EMERGENT trials, the incidence of broadly defined, treatment-related EPS with KarXT was low (1.5% KarXT vs 0.3% placebo); this low rate may be related to KarXT not binding to D_2 dopamine receptors
- Although akathisia was the most commonly reported EPS TEAE in the short-term EMERGENT efficacy trials and was more common with KarXT than placebo (2.4% vs 0.9%), akathisia TEAEs deemed related to trial medication were reported in only 0.6% of participants in the KarXT group vs 0.3% of participants in the placebo group
- Moreover, KarXT was not associated with clinically meaningful changes in SAS, BARS, or AIMS scores over 5 weeks of treatment compared with placebo
- Together with the pooled efficacy results showing a clinically meaningful reduction in the positive and negative symptoms of schizophrenia, these results suggest that, if approved, KarXT may provide a therapeutic option with a low risk for EPS AEs that can be associated with the current standard of care

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Disclosures

PJW was employed by Karuna Therapeutics until April 2023. Since May 2023, PJW has received consulting fees from Alkermes, Lyndra, and MapLight Therapeutics, and is a speaker for Teva. KN, CW, CS, IK, ACM, AC, SMP, and SKB are employees of and hold equity in Karuna Therapeutics.

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