Safety and Tolerability of KarXT (Xanomeline–Trospium): Pooled Results From the Randomized, Double-Blind, Placebo-Controlled EMERGENT Trials

Stephen K. Brannan,[1] Andrew J. Cutler,[2] Sharon Sawchak,[1] Judith Kando,[1] Andrew C. Miller,[1] Amy Claxton,[1] Steven M. Paul,[1] Inder Kaul[1]

[1]Karuna Therapeutics, Boston, MA; [2]SUNY Upstate Medical University, Lakewood Ranch, FL

NEI Congress
Poster 99

Introduction

- Current antipsychotics, all of which have direct D_2 dopamine receptor blocking activity, are associated with well-known efficacy and tolerability limitations[1,2]; a high unmet need remains for more effective, better tolerated treatment options with a different mechanism for people with schizophrenia
- KarXT (xanomeline–trospium chloride) is a potential new treatment for people with schizophrenia with a novel mechanism of action based on muscarinic receptor agonism
- In the 5-week, randomized, 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

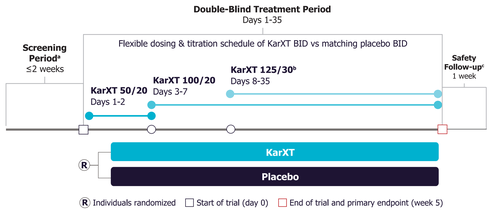
Objective

- To evaluate the safety and tolerability of KarXT in the treatment of acute psychosis in people with schizophrenia using pooled data from the EMERGENT trials

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 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
- All safety analyses were conducted in the safety population, defined as all randomized participants who received ≥1 dose of trial medication
- Treatment-emergent adverse events (TEAEs) were defined as events that began after the administration of the trial medication (either KarXT or placebo)
- Treatment-related adverse events (AEs) were defined as events the investigator considered possibly, probably, or definitely related to trial drug, as well as events with unknown relationship

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.

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 baseline demographics and characteristics between treatment groups (**Table 1**)

Table 1. Baseline Demographics and Characteristics (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.

Safety and Tolerability

- Across the EMERGENT trials, KarXT was generally well tolerated in people with schizophrenia experiencing acute psychosis
- Across the EMERGENT trials, 51.8% of people in the KarXT group compared with 29.4% in the placebo group reported ≥1 treatment-related AE (**Table 2**)
- Overall discontinuation rates (27.6% vs 22.7%) and rates of discontinuation due to TEAEs (5.6% vs 4.7%) were similar between KarXT and placebo groups
- The most common TEAEs in the KarXT group vs placebo group were nausea (18.5% vs 3.8%), constipation (17.1% vs 6.1%), dyspepsia (15.9% vs 4.7%), vomiting (13.5% vs 1.7%), headache (10.9% vs 10.5%), hypertension (8.5% vs 1.7%), abdominal pain (5.9% vs 2.9%), somnolence (5.3% vs 4.4%), dry mouth (5.0% vs 1.5%), and tachycardia (5.0% vs 2.3%), all of which were mild or moderate in severity (**Table 3**)
  - One serious treatment-related AE (psychotic disorder) was reported in the KarXT group
  - The most common treatment-related AEs reflect the activity of xanomeline and trospium at muscarinic receptors
- KarXT was not associated with weight gain or metabolic changes
  - Mean change from baseline to week 5 in body weight was 1.41±3.18 kg in the KarXT group compared with 1.94±5.00 kg in the placebo group
  - 13/245 participants (5.3%) in the KarXT group compared with 30/264 participants (11.4%) in the placebo group had an increase in body weight of ≥7%
- KarXT was not associated with clinically meaningful changes from baseline to week 5 in movement disorder scales
  - Simpson-Angus Scale score: KarXT, -0.1±0.62; placebo, -0.1±0.63
  - Barnes Akathisia Rating Scale score: KarXT, -0.1±0.90; placebo, -0.1±0.84
  - Abnormal Involuntary Movement Scale score: KarXT, 0.0±0.66; placebo, 0.0±0.15
- Prolactin levels were similar between treatment groups over the 5-week treatment period (mean change from baseline to week 5: KarXT, 0.75±16.45 ng/L; placebo, -1.38±16.49 ng/L) (**Figure 2**)

Table 2. Treatment-Related AEs During the 5-Week Treatment Period (Safety Population)

Variable	KarXT (n=340)	Placebo (n=343)
Any treatment-related AE, n (%)	176 (51.8)	101 (29.4)
Serious treatment-related AE, n (%)	1 (0.3)[a]	0
Treatment-related AEs reported in ≥2% of people in the KarXT group and at least twice the placebo rate, n (%)		
Nausea	58 (17.1)	11 (3.2)
Constipation	51 (15.0)	18 (5.2)
Dyspepsia	41 (12.1)	8 (2.3)
Vomiting	37 (10.9)	3 (0.9)
Hypertension[b]	20 (5.9)	4 (1.2)
Dry mouth	17 (5.0)	5 (1.5)
Tachycardia	16 (4.7)	7 (2.0)
Abdominal pain	16 (4.7)	5 (1.5)
Dizziness	15 (4.4)	6 (1.7)
Gastroesophageal reflux disease	9 (2.6)	1 (0.3)
Vision blurred	8 (2.4)	1 (0.3)

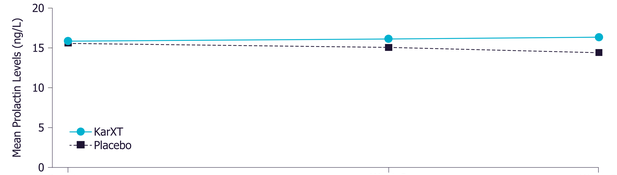
[a]Psychotic disorder (n=1). [b]Hypertension is the MedDRA preferred term and is not necessarily reflective of clinical hypertension.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

Table 3. Severity of the Most Common TEAEs[a]

Variable, no. TEAE (%)	KarXT (n=340)		Placebo (n=343)	
	Mild	Moderate	Mild	Moderate
Nausea	48 (14.1)	15 (4.4)	12 (3.5)	1 (0.3)
Constipation	47 (13.8)	11 (3.2)	17 (5.0)	4 (1.2)
Dyspepsia	38 (11.2)	16 (4.7)	15 (4.4)	1 (0.3)
Vomiting	31 (9.1)	15 (4.4)	4 (1.2)	2 (0.6)
Headache	29 (8.5)	8 (2.4)	28 (8.2)	8 (2.3)
Hypertension	18 (5.3)	11 (3.2)	5 (1.5)	1 (0.3)
Abdominal pain	14 (4.1)	6 (1.8)	9 (2.6)	2 (0.6)
Somnolence	10 (2.9)	8 (2.4)	12 (3.5)	3 (0.9)
Dry mouth	12 (3.5)	5 (1.5)	5 (1.5)	0
Tachycardia	13 (3.8)	4 (1.2)	7 (2.0)	1 (0.3)

[a]TEAEs occurring in ≥5% of people in the KarXT group.
TEAE, treatment-emergent adverse event.

Figure 2. Prolactin Levels Over the 5-Week Treatment Period



Prolactin reference range: males <20 ng/mL, nonpregnant females <25 ng/mL.

Conclusions

- In pooled analyses from the EMERGENT trials, KarXT was generally well tolerated in people with schizophrenia experiencing acute psychosis
- Rates of discontinuation due to TEAEs were similar between KarXT and placebo groups
- The most common treatment-related AEs in the KarXT group were consistent with the known activity of xanomeline and trospium at muscarinic receptors, and the majority were mild in severity
- KarXT was not associated with weight gain, adverse changes in metabolic parameters, or extrapyramidal symptoms, which are common AEs associated with currently available antipsychotic medications
- These findings, together with the efficacy results showing a clinically meaningful reduction in the symptoms of schizophrenia, support the potential of KarXT to be the first in a new class of antipsychotic medications based on muscarinic receptor agonism and an efficacious and well-tolerated alternative to currently available antipsychotics if approved

References

1. McCutcheon RA, et al. *JAMA Psychiatry*. 2020;77(2):201-210.
2. Leucht S, et al. *Am J Psychiatry*. 2017;174(10):927-942.
3. Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-726.
4. Correll CU, et al. Presented at: ECNP; Oct 15-18, 2022; Vienna, Austria. Poster P.0193.
5. Tamminga C, et al. Presented at: SIRS; May 11-15, 2023; Toronto, Canada. Oral presentation.

Disclosures

SKB, SS, JK, ACM, AC, SMP, and IK are employees of and hold equity in Karuna Therapeutics. AJC is an employee and board member of the Neuroscience Education Institute and has received advising, consulting, and/or speaking fees in the prior 24 months from AbbVie, Acadia, Akili Interactive, Alfasigma, Alkermes, Axsome, Biogen, BioXcel, Boehringer Ingelheim, Cerevel, Idorsia, Intra-Cellular Therapies, Janssen, Karuna Therapeutics, Lundbeck, Luye, Neumora, Neurocrine, Noven, Otsuka, Pear Therapeutics, Relmada, Sage Therapeutics, Sunovion, Supernus, Teva, and VistaGen.

Acknowledgments

The authors thank Matthew Jacobson, CMPP, and Paula Stuckart of Apollo Medical Communications, part of Helios Global Group, for medical writing and editorial support, which was funded by Karuna Therapeutics. The EMERGENT trials were sponsored by Karuna Therapeutics.