Onset, Duration, and Severity of Adverse Events With KarXT (Xanomeline–Trospium) in the Randomised, Double-Blind, Placebo-Controlled Phase 3 EMERGENT-3 Trial

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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 of action for people with schizophrenia
- KarXT combines the dual M_1/M_4 preferring muscarinic receptor agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride with the goal of preserving xanomeline's beneficial effects in the central nervous system while ameliorating side effects due to peripheral muscarinic receptor activation
- In the 5-week, randomised, double-blind, placebo-controlled EMERGENT-1 (NCT03697252),[3] EMERGENT-2 (NCT04659161),[4] and EMERGENT-3 (NCT04738123)[5] trials, KarXT significantly improved symptoms of schizophrenia compared with placebo as measured by change in Positive and Negative Syndrome Scale total score at week 5 and was generally well tolerated in people with schizophrenia experiencing acute psychosis

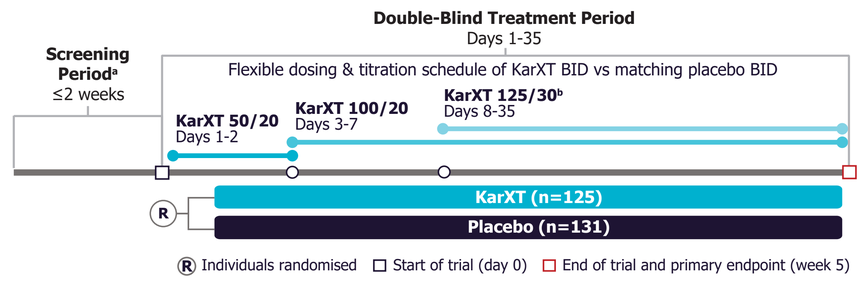
Objective

- To characterise the onset, duration, severity, and number needed to harm (NNH) for the most common treatment-emergent adverse events (TEAEs) with KarXT in EMERGENT-3

Methods

- EMERGENT-3 was a randomised, double-blind, placebo-controlled, inpatient, phase 3 trial of KarXT conducted in people with schizophrenia experiencing acute psychosis (**Figure 1**)
- Adults aged 18-65 years with a confirmed *DSM-5* diagnosis of schizophrenia and recent worsening of psychotic symptoms warranting hospitalisation were enrolled
- Eligible participants were randomised 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
- Post hoc analyses were conducted in the safety population, defined as all randomised participants who received ≥1 dose of trial medication, and employed descriptive statistics
- The duration of TEAEs was calculated as TEAE end date minus TEAE start date plus 1, except for TEAEs that were ongoing at the end of the trial, in which case duration was imputed using each participant's end-of-trial date instead of TEAE end date
- The NNH for the most common TEAEs was calculated as 1 divided by the difference in TEAE incidence rates between placebo and KarXT

Figure 1. EMERGENT-3 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 a clinician.
BID, twice daily.

Results

Participants

- A total of 256 participants (KarXT, n=125; placebo, n=131) at 18 sites in the United States and 12 sites in Ukraine were enrolled; 253 participants (KarXT, n=125; placebo, n=128) were included in the safety population
- There were no meaningful differences in baseline demographics and characteristics between treatment groups

Overall Safety and Tolerability

- KarXT was generally well tolerated (**Table 1**), with a side effect profile substantially consistent with prior trials
- Overall discontinuation rates were similar between the KarXT and placebo arms (36.8% vs 29.0%)
- The most common TEAEs occurring in ≥5% of participants in the KarXT group and at a >2-fold greater incidence than in the placebo group were nausea (19.2% vs 1.6%), dyspepsia (16.0% vs 1.6%), vomiting (16.0% vs 0.8%), and constipation (12.8% vs 3.9%)
- KarXT was not associated with weight gain or changes in measures of extrapyramidal motor symptoms (EPS) (**Table 1**)

Table 1. Safety and Tolerability During the 5-Week Treatment Period (Safety Population)

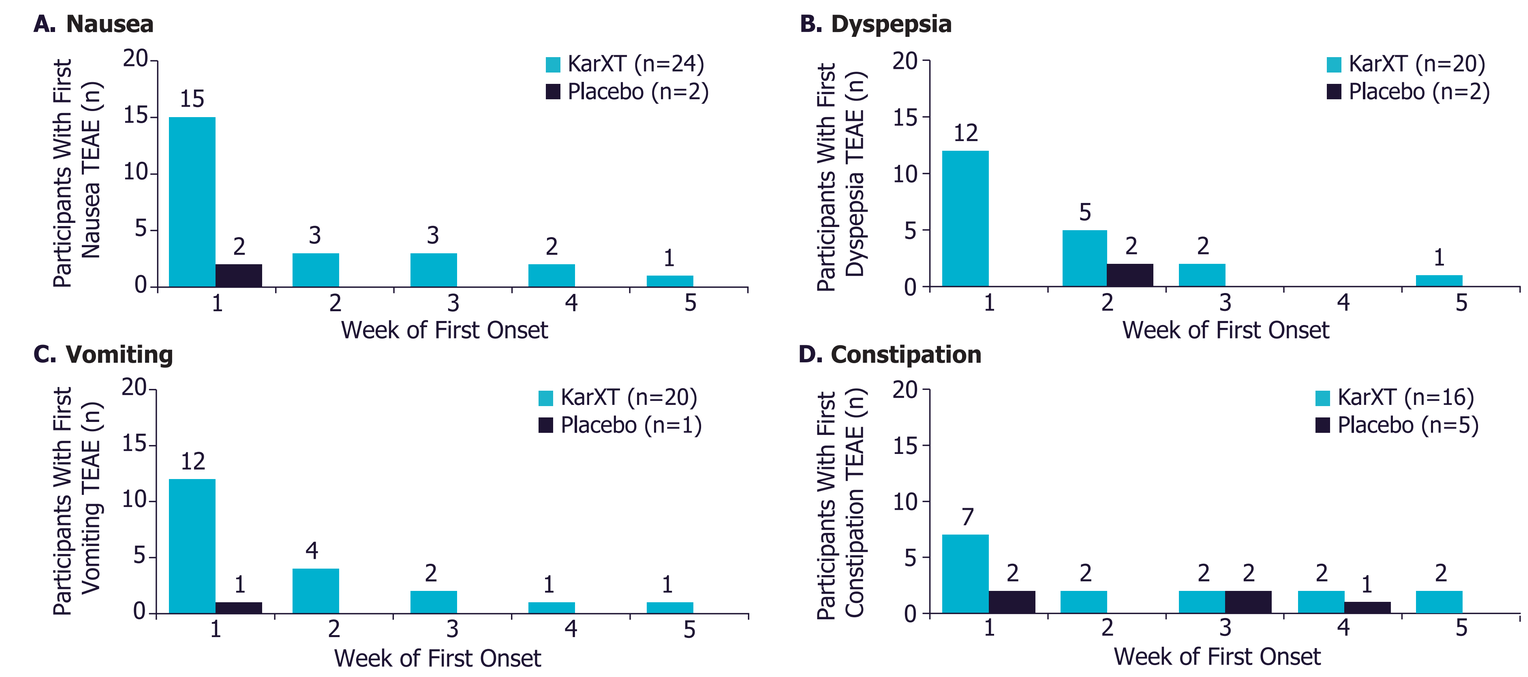
Variable	KarXT (n=125)	Placebo (n=128)
Any TEAE, n (%)	88 (70.4)	64 (50.0)
Serious TEAE,[a] n (%)	1 (0.8)	0
TEAE leading to discontinuation, n (%)	8 (6.4)	7 (5.5)
TEAE occurring in ≥5% of participants in the KarXT group, n (%)		
Nausea	24 (19.2)	2 (1.6)
Dyspepsia	20 (16.0)	2 (1.6)
Vomiting	20 (16.0)	1 (0.8)
Constipation	16 (12.8)	5 (3.9)
Headache	14 (11.2)	15 (11.7)
Hypertension[b]	8 (6.4)	2 (1.6)
Insomnia	7 (5.6)	10 (7.8)
Diarrhoea	7 (5.6)	1 (0.8)
Body weight: mean change from baseline to week 5 ±SD, kg	1.41±3.37	2.0±3.08
Body weight: ≥7% increase from baseline to week 5, n/N (%)	5/78 (6.4)	12/92 (13.0)
Simpson-Angus Scale score: mean change from baseline to week 5 ±SD	-0.1±0.56	-0.1±0.36
Barnes Akathisia Rating Scale score: mean change from baseline to week 5 ±SD	-0.1±0.75	-0.1±0.88

[a]One serious TEAE of gastroesophageal reflux disease was reported.
[b]Hypertension is the MedDRA preferred term and is not necessarily reflective of clinical hypertension.
MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation; TEAE, treatment-emergent adverse event.

Onset, Duration, and Severity of the Most Common TEAEs

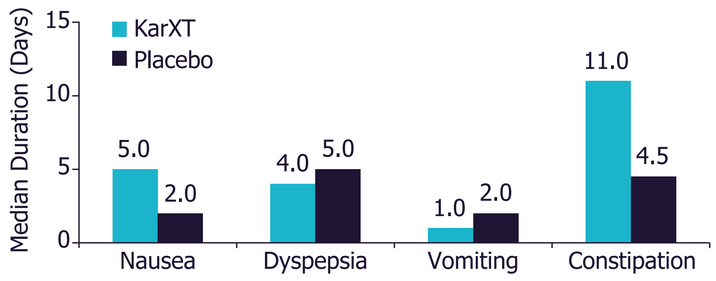
- Nausea, dyspepsia, vomiting, and constipation with KarXT generally began within the first 2 weeks of treatment (**Figure 2**); the majority of these TEAEs were mild in severity (**Table 2**) and transient in nature, with median durations ranging from 1 day for vomiting to 11 days for constipation (**Figure 3**)
- Few TEAEs of nausea, dyspepsia, vomiting, or constipation led to trial discontinuation
  - Overall, 2.4%, 0.8%, 0%, and 0% of KarXT group participants and 0%, 0%, 0%, and 0% of placebo group participants discontinued the trial due to nausea, dyspepsia, vomiting, or constipation, respectively
- The estimated NNH (95% confidence interval) for KarXT vs placebo was 6 (5-10) for nausea, 7 (5-14) for dyspepsia, 7 (5-12) for vomiting, and 12 (7-47) for constipation (**Table 2**)

Figure 2. Onset of the Most Common TEAEs



TEAE, treatment-emergent adverse event.

Figure 3. Duration of the Most Common TEAEs



Including ongoing TEAEs at trial end.
TEAE, treatment-emergent adverse event.

Table 2. Severity of the Most Common TEAEs

	KarXT (n=125) n/N (%)		Placebo (n=128) n/N (%)		NNH (95% CI)
	Mild	Moderate	Mild	Moderate	
Nausea	16/24 (67)	8/24 (33)	2/2 (100)	0/2 (0)	6 (5-10)
Dyspepsia	15/20 (75)	5/20 (25)	2/2 (100)	0/2 (0)	7 (5-14)
Vomiting	14/20 (70)	6/20 (30)	1/1 (100)	0/1 (0)	7 (5-12)
Constipation	12/16 (75)	4/16 (25)	4/5 (80)	1/5 (20)	12 (7-47)

CI, confidence interval; NNH, number needed to harm; TEAE, treatment-emergent adverse event.

Conclusions

- In EMERGENT-3, KarXT was generally well tolerated and associated with a low overall adverse event burden
- The most common TEAEs in the KarXT group (nausea, dyspepsia, vomiting, and constipation) were consistent with the known activity of xanomeline and trospium at muscarinic receptors
  - The majority of these TEAEs first occurred within the first 2 weeks of treatment, were mild in severity, and were transient in nature
- KarXT was not associated with weight gain or changes in measures of EPS
- If approved, KarXT has the potential to be the first in a new class of treatments for people with schizophrenia based on muscarinic receptor agonism without direct D_2 dopamine receptor blocking activity

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Disclosures

CAT is a consultant to and holds equity in Karuna Therapeutics, is a consultant to and holds equity in KyNexis, and is a consultant to Merck and Sunovion. CUC has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo Pharma, Boehringer Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Gedeon Richter, Hikma, Holmusk, Intra-Cellular Therapies, Janssen/Johnson & Johnson, Karuna Therapeutics, LB Pharma, Lundbeck, MedAvante-ProPhase, MedinCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine Biosciences, Newron, Noven, Otsuka, Pharmabrain, PPD, Recordati, Relmada, Reviva, ROVI, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris; provided expert testimony for Janssen and Otsuka; served on a data safety monitoring board for Lundbeck, Relmada, Reviva, ROVI, Supernus, and Teva; has received grant support from Janssen and Takeda; received royalties from UpToDate; and is a stock option holder of Cardio Diagnostics, LB Pharma and Mindpax. DPW has received grants/research support from AbbVie, Acadia, Alkermes, Allergan, Avanir, Biogen, Boehringer Ingelheim, Cerevel, Indivior, Intra-Cellular Therapies, Janssen, Johnson & Johnson, Karuna Therapeutics, Lundbeck, Lupin, Lyndra, Novartis, Noven, Otsuka, Pfizer, Roche, Sunovion, and Takeda; served as a consultant to Biogen, Boehringer Ingelheim, Janssen, Lyndra, and Otsuka. IK, ACM, and SKB are employees of and hold equity in Karuna Therapeutics.

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