Supplemental Online Content

Kaul I, Sawchak S, Walling DP, et al. Efficacy and safety of xanomeline–trospium in schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. Published online May 1, 2024. doi:10.1001/jamapsychiatry.2024.0785

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Inclusion and Exclusion Criteria

Inclusion criteria

- Age 18 to 65 years, inclusive, at screening
- Capable of providing informed consent
  - Signed informed consent form
  - Fluent (oral and written) in local language to consent
- Primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (*DSM-5)* criteria and confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies version 7.0.2
- Experiencing an acute exacerbation or relapse of psychotic symptoms, with onset <2 months before screening
  - Required hospitalization for this acute exacerbation or relapse of psychotic symptoms
  - If already an inpatient at screening, had been hospitalized for <2 weeks for the current exacerbation at the time of screening
- Positive and Negative Syndrome Scale (PANSS) total score between 80 and 120, inclusive. Score of ≥4 (moderate or greater) for ≥2 of the following positive scale (P) items
  - Item 1 (P1; delusions)
  - Item 2 (P2; conceptual disorganization)
  - Item 3 (P3; hallucinatory behavior)
  - Item 6 (P6; suspiciousness/persecution)
- No change (improvement) in PANSS total score between screening and baseline of >20%
- Clinical Global Impression–Severity score of ≥4 at screening and baseline
- Off lithium therapy for >2 weeks before baseline and free of all oral antipsychotic medications for ≥5 half-lives or 1 week, whichever was longer, before baseline
- Participants taking a long-acting injectable antipsychotic were not to have received a dose of medication for ≥12 weeks (24 weeks for paliperidone palmitate) before baseline
- Willing and able to be confined to an inpatient setting for the trial duration, follow instructions, and comply with the protocol requirements
- BMI between 18 and ≤40 kg/m^2, inclusive
- Participant resided in a stable living situation and was anticipated to return to that same stable living situation after discharge, in the opinion of the investigator
- Had an identified, reliable informant if the trial participant had not been a patient of the investigator for ≥1 year
- Willing to adhere to defined contraception guidelines

Exclusion criteria

- Any primary *DSM-5* disorder other than schizophrenia within 12 months before screening
  - Mild substance abuse disorder within the 12 months before screening, unless agreed upon with the medical monitor
- Newly diagnosed or experiencing first treated episode of schizophrenia
- History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would have jeopardized the safety of the participant or the validity of the trial results
- Participants with HIV, cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on either medical history or liver function test results
- History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma
- History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months
- Risk for suicidal behavior during the trial as determined by the investigator's clinical assessment and Columbia Suicide Severity Rating Scale (C-SSRS), as confirmed by the following
  - Answered "Yes" on items 4 or 5 (C-SSRS–ideation) with the most recent episode occurring within the 2 months before screening or answered "Yes" to any of the 5 items (C-SSRS–behavior) with an episode occurring within the 12 months before screening. Nonsuicidal, self-injurious behavior was not exclusionary
- Clinically significant abnormal finding on the physical examination, medical history, electrocardiogram, or clinical laboratory results at screening
- Could not currently (within 5 half-lives or 1 week, whichever was longer, before baseline) have received oral antipsychotic medications, monoamine oxidase inhibitors, anticonvulsants, tricyclic antidepressants, selective serotonin reuptake inhibitors, or any other psychoactive medications, except for as-needed anxiolytics
- Pregnant, lactating, or <3 months postpartum
- Positive test for SARS-CoV-2 (COVID-19) within 2 weeks before screening and at screening
- Extreme concerns relating to global pandemics, such as COVID-19, which preclude trial participation
- Had psychiatric hospitalization(s) for >30 days (cumulative) during the 90 days before screening
- History of treatment resistance to schizophrenia medications, defined as failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) or required clozapine within the last 12 months
- Prior exposure to KarXT
- Experienced any adverse effects due to xanomeline or trospium chloride
- Risk of violent or destructive behavior
- Current involuntary hospitalization or incarceration

eTable 1. Efficacy Measures at Week 5 (mITT Population)

Variable	KarXT (n = 114)	Placebo (n = 120)	Difference (95% CI)	Cohen's *d*	*P* value
Primary endpoint					
PANSS total score, LSM change (SE) from baseline	-20.6 (1.6)	-12.2 (1.6)	-8.4 (-12.4 to -4.3)	0.60	<.0001
Secondary outcome measures					
PANSS positive symptom subscale score, LSM change (SE) from baseline	-7.1 (0.5)	-3.6 (0.5)	-3.5 (-4.7 to -2.2)	0.80	<.0001
PANSS negative symptom subscale score, LSM change (SE) from baseline	-2.7 (0.4)	-1.8 (0.4)	-0.8 (-1.9 to 0.2)	0.23	.1224
PANSS Marder negative factor score, LSM change (SE) from baseline	-3.5 (0.5)	-2.7 (0.5)	-0.8 (-2.1 to 0.4)	0.19	.1957
CGI-S scale score, LSM change (SE) from baseline	-1.1 (0.1)	-0.6 (0.1)	-0.5 (-0.8 to -0.3)	0.63	<.0001
PANSS responders (≥30% reduction from baseline in PANSS total score),[a] n/N (%)	40/79 (50.6%)	23/91 (25.3%)	25.4% (10.8 to 38.6)		.0056

[a] Floor-adjusted total score (total score minus 30); last observation carried forward. Assessed in participants with available week 5 scores.

Abbreviations: CGI-S, Clinical Global Impression–Severity; LSM, least squares mean; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale.

eTable 2. Primary and Supportive Analyses for Primary End Point: Change From Baseline at Week 5 in PANSS Total Score

	KarXT		Placebo		Difference	
Analysis	n	LSM change (SE) from baseline	n	LSM change (SE) from baseline	**Difference (95% CI)**	***P* value**
Primary analysis (mITT)	114	-20.6 (1.6)	120	-12.2 (1.6)	-8.4 (-12.4 to -4.3)	<.0001
Completer analysis	79	-20.8 (1.6)	91	-13.6 (1.6)	-7.1 (-11.2 to -3.0)	.0008
Placebo-based MI (mITT)	114	-18.7 (1.6)	120	-11.6 (1.6)	-7.1 (-11.3 to -2.8)	.0010
Post-hoc analysis (ITT)	125	-20.6 (1.6)	131	-12.2 (1.6)	-8.4 (-12.4 to -4.3)	<.0001

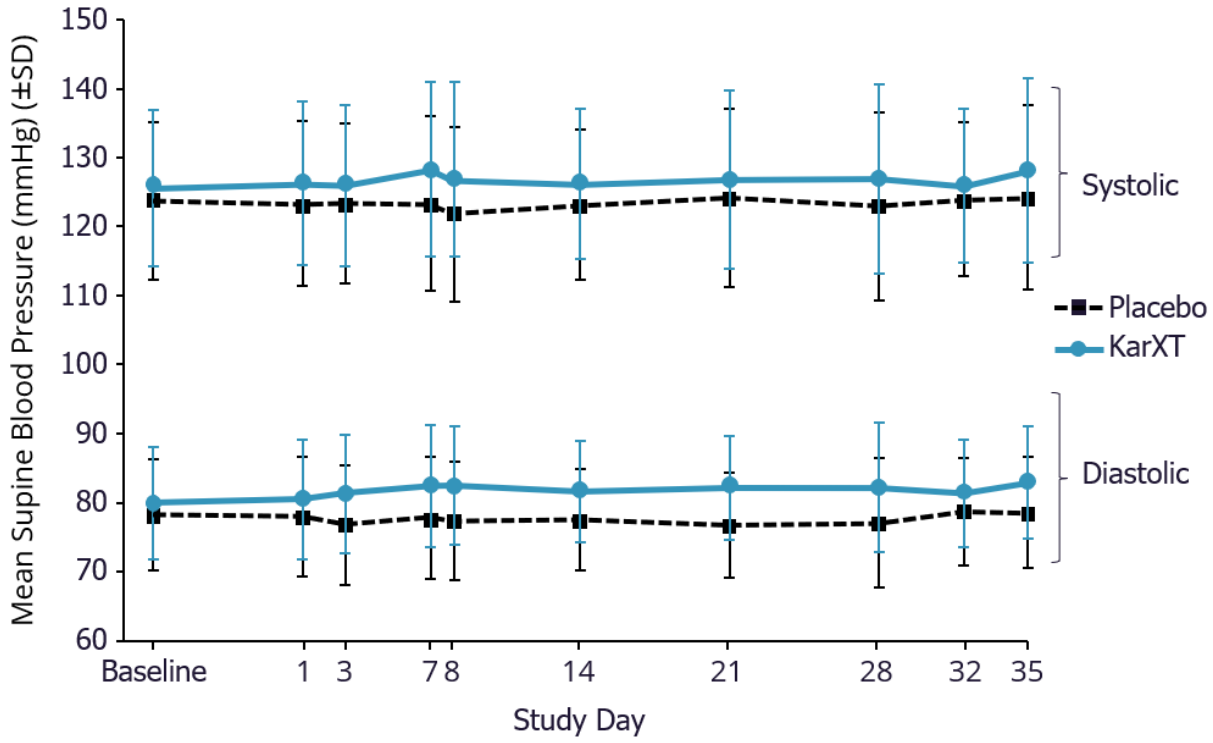
Abbreviations: ITT, intent-to-treat; LSM, least squares mean; MI, multiple imputation; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

eTable 3. Treatment-Emergent Adverse Events Leading to Trial Discontinuation

Variable	KarXT (n = 125)	Placebo (n = 128)
At least one TEAE leading to discontinuation, n (%)	8 (6.4)	7 (5.5)
Psychiatric disorders		
Schizophrenia	0	5 (3.9)
Insomnia	1 (0.8)	1 (0.8)
Mental disorder	0	1 (0.8)
Gastrointestinal disorders		
Nausea	3 (2.4)	0
Abdominal pain	1 (0.8)	0
Diarrhea	1 (0.8)	0
Gastroesophogeal reflux disease	1 (0.8)	0
Vomiting	1 (0.8)	0
General disorders and administration site conditions		
Asthenia	1 (0.8)	0
Chest discomfort	1 (0.8)	0
Investigations		
Heart rate increased	1 (0.8)	0
Hepatic enzyme increased	1 (0.8)	0
Metabolism and nutrition disorders		
Decreased appetite	1 (0.8)	0
Nervous system disorders		
Dyskinesia	1 (0.8)	0
Renal and urinary disorders		
Dysuria	1 (0.8)	0
Skin and subcutaneous tissue disorders		
Angioedema	1 (0.8)	0

Abbreviation: TEAE, treatment-emergent adverse event.

eFigure. Mean Systolic and Diastolic Blood Pressure Measures Recorded at 2 Hours Post Dose (C_{max})



During treatment, beginning on day 1, blood pressure was measured 2 (±1) hours after morning dose of trial treatment.
Abbreviation: C_{max}, maximum concentration