# Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline–trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial

*Inder Kaul, Sharon Sawchak, Christoph U Correll, Rishi Kakar, Alan Breier, Haiyuan Zhu, Andrew C Miller, Steven M Paul, Stephen K Brannan*

*Lancet* 2024; 403: 160–70

Published Online December 14, 2023 https://doi.org/10.1016/S0140-6736(23)02190-6

This online publication has been corrected. The corrected version first appeared at thelancet.com on May 30, 2024

See Comment page 120

**Karuna Therapeutics, Boston, MA, USA** (I Kaul MD, S Sawchak RN, H Zhu PhD, A C Miller PhD, S M Paul MD, S K Brannan MD); **Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY, USA** (Prof C U Correll MD); **Departments of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA** (C U Correll); **Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany** (C U Correll); **Segal Trials, Miami Lakes, FL, USA** (R Kakar MD); **Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA** (Prof A Breier MD)

Correspondence to: Dr Steven M Paul, Karuna Therapeutics, Boston, MA, USA **spaul@karunatx.com**

## Summary

**Background** New treatments with new mechanisms are urgently needed for people with schizophrenia. Xanomeline is a dual $M_1$ and $M_4$-preferring muscarinic receptor agonist that does not block $D_2$ dopamine receptors, unlike all currently approved treatments for schizophrenia. Xanomeline–trospium (KarXT) combines xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride with the goal of ameliorating xanomeline-related adverse events associated with peripheral muscarinic receptors. The EMERGENT-2 trial aimed to assess the efficacy and safety of KarXT in people with schizophrenia experiencing acute psychosis.

**Methods** EMERGENT-2 was a randomised, double-blind, placebo-controlled, flexible-dose, 5-week, inpatient, phase 3 trial in people with schizophrenia. Participants were adults aged 18–65 years with a diagnosis of schizophrenia who had a recent worsening of psychosis warranting hospital admission, a Positive and Negative Syndrome Scale (PANSS) score of 80 or higher, and a Clinical Global Impression-Severity score of 4 or higher. The participants were recruited from 22 inpatient sites in the USA, and were randomly assigned (1:1) to KarXT or placebo twice per day. Participants randomly assigned to KarXT received 50 mg xanomeline and 20 mg trospium twice per day for the first 2 days and then 100 mg xanomeline and 20 mg trospium twice per day for days 3–7. Beginning on day 8, KarXT dosing was flexible with an optional increase to 125 mg xanomeline and 30 mg trospium twice per day and the option to return to 100 mg xanomeline and 20 mg trospium based on tolerability. The primary endpoint was change from baseline to week 5 in PANSS total score. Efficacy analyses used the modified intention-to-treat population (all randomly assigned participants who received at least one trial medication dose and had at least one post-baseline PANSS assessment). Least squares mean change from baseline, SE, and least squares mean difference between the KarXT and placebo groups at week 5, along with the 95% CI and two-sided p values were calculated for the primary and secondary continuous efficacy endpoints. Safety analyses included all participants receiving at least one trial medication dose and used descriptive statistics. This trial is registered with ClinicalTrials.gov (NCT04659161).

**Findings** From Dec 16, 2020, to April 13, 2022, of 407 people who were screened, 252 participants meeting enrolment criteria were randomly assigned to the KarXT (n=126) or placebo (n=126). Baseline PANSS total scores were 98·3 (KarXT; n=126) and 97·9 (placebo; n=125). The trial met the primary endpoint with a mean change from baseline to week 5 in PANSS total score that favoured KarXT (–21·2 points, SE 1·7) versus placebo (–11·6 points, 1·6; least squares mean difference –9·6; 95% CI –13·9 to –5·2; p<0·0001, Cohen's *d* effect size=0·61). All secondary endpoints were also met, and favoured KarXT versus placebo (p<0·05). The most common adverse events with KarXT versus placebo were constipation (27 [21%] *vs* 13 [10%]), dyspepsia (24 [19%] *vs* 10 [8%]), headache (17 [14%] *vs* 15 [12%]), nausea (24 [19%] *vs* seven [6%]), vomiting (18 [14%] *vs* one [1%]), hypertension (12 [10%] *vs* one [1%]), dizziness (11 [9%] *vs* four [3%]), gastro-oesophageal reflux disease (eight [6%] *vs* zero [0%]), and diarrhoea (seven [6%] *vs* four [3%]). Treatment-emergent adverse event rates of extrapyramidal motor symptoms (KarXT, zero [0%] *vs* placebo, zero [0%]), akathisia (one [1%] *vs* one [1%]), weight gain (zero [0%] *vs* one [1%]), and somnolence (six [5%] *vs* five [4%]) were similar between the KarXT and placebo groups, as were adverse event-related discontinuation rates (nine [7%] *vs* seven [6%]).

**Interpretation** In the EMERGENT-2 trial, KarXT was effective in reducing positive and negative symptoms and was generally well tolerated. These results support the potential for KarXT to represent a new class of effective and well tolerated antipsychotic medicines based on activating muscarinic receptors, not the $D_2$ dopamine receptor-blocking mechanism of all current antipsychotic medications. Results from additional trials, including the identical EMERGENT-3 trial and the 52-week, open-label EMERGENT-4 and EMERGENT-5 trials, will provide additional information on the efficacy and safety of KarXT in people with schizophrenia.

**Funding** Karuna Therapeutics.

## Research in context

### Evidence before this trial

We searched PubMed from inception to Dec 6, 2020 for randomised controlled trials published in English using the search term "xanomeline". We identified two studies. In previous randomised controlled trials, xanomeline demonstrated antipsychotic activity in people with schizophrenia or Alzheimer's disease, but its clinical development was limited by gastrointestinal adverse events. Phase 1 and 2 trials demonstrated that adding the peripherally restricted muscarinic receptor antagonist trospium chloride reduced the frequency and severity of gastrointestinal adverse events with xanomeline. In the phase 2 EMERGENT-1 trial in people with schizophrenia experiencing acute psychosis, KarXT (xanomeline-trospium) demonstrated antipsychotic efficacy and was generally safe and well tolerated.

### Added value of this trial

KarXT again demonstrated efficacy and tolerability in people with schizophrenia experiencing acute psychosis in the EMERGENT-2 trial. In this randomised, double-blind, placebo-controlled, phase 3 trial, KarXT was associated with a significant and clinically meaningful reduction in Positive and Negative Syndrome Scale total score, improvement in several secondary outcome measures, and was generally safe and well tolerated.

### Implications of all the available evidence

This trial showed that KarXT was effective in reducing positive and negative symptoms and generally well tolerated in people with schizophrenia. In the EMERGENT-2 trial, the most common side-effects with KarXT were constipation, dyspepsia, nausea, vomiting, hypertension, dizziness, and gastro-oesophageal reflux disease, which reflect the mechanisms of xanomeline and trospium. KarXT demonstrated a distinctive safety and tolerability profile and was not associated with many of the adverse events typically associated with current antipsychotic treatments, including extrapyramidal motor symptoms, weight gain, changes in lipid and glucose parameters, and somnolence. KarXT has the potential to be the first of a new class of effective and well tolerated antipsychotic medicines on the basis of activating muscarinic receptors, as opposed to the $D_2$ dopamine-receptor blocking activity associated with all current antipsychotic medications.

## Introduction

Schizophrenia is a serious, disabling brain disorder that often begins in late adolescence or early adulthood and is typically followed by a chronic course marked by relapses, hospital admissions, and substantial morbidity and mortality.[1,2] It is a leading cause of disability and years of life lost globally.[3,4] Schizophrenia is also associated with one of the highest mortality rates among all psychiatric illnesses, a life expectancy reduced by 15–30 years, and an estimated lifetime suicide rate of 4·9%.[5–8]

The primary symptom domains of schizophrenia are positive symptoms (eg, delusions and hallucinations), negative symptoms (eg, constricted affect and asociality), and cognitive symptoms. Cognitive symptoms are a core clinical feature and people with schizophrenia commonly show poor performance on measures of executive function, long-term memory, sustained attention, and general intellectual impairment, often at illness onset.[2] The mainstays for treating schizophrenia are antipsychotic drugs. More than 30 antipsychotic drugs have been approved by the European Medicines Agency, the US Food and Drug Administration, and other regulatory authorities,[9] and all act as direct or functional (eg, via partial agonism) $D_2$ dopamine receptor antagonists.[10] Many have additional effects, including antagonism of serotonin (particularly 5-hydroxy-tryptamine 2A), adrenergic, and histaminergic receptors.[10] Currently available antipsychotic drugs are generally divided into two classes, first and second generation, with second-generation antipsychotic drugs in predominant use today. The largely conserved pharmacology across available antipsychotic drugs, however, results in similar outcomes that are inadequate for many people with schizophrenia. Antipsychotic drugs have established efficacy in treating only positive symptoms, but have limited efficacy for negative or cognitive symptoms. Moreover, approximately 30% of people with schizophrenia are treatment resistant to antipsychotic drugs, defined as not responding to two or more antipsychotic drugs, and many more derive only partial positive symptom benefit.[11] One study found that almost one of four people with first-episode psychosis or schizophrenia will develop treatment-resistant schizophrenia during the early stages of treatment.[12] Antipsychotic drugs are a heterogenous class of medication and can cause a range of substantial short-term and long-term side-effects, including extrapyramidal motor symptoms or akathisia, tardive dyskinesia, hyperprolactinemia, weight gain, metabolic disturbances, and somnolence or sedation, each of which contributes to substantial morbidity, an estimated non-adherence rate between 40% and 50%, and subsequent relapses.[9,13] Some of these side-effects emerge after longer-term use. An important unmet medical need exists for people with schizophrenia, and new treatments with novel mechanisms are urgently needed.

Increasing evidence suggests that muscarinic acetylcholine receptors are involved in schizophrenia pathophysiology, representing promising new treatment targets for schizophrenia.[14] Xanomeline is an oral muscarinic receptor agonist devoid of direct $D_2$ dopamine receptor effects.[15] It is a preferential agonist of $M_1$ and $M_4$ muscarinic receptors, which have been implicated in schizophrenia.[14] In two previous placebo-controlled clinical trials in Alzheimer's disease[16] and schizophrenia,[17] xanomeline was associated with a reduction in psychotic symptoms and improved

cognition. However, xanomeline was associated with high rates of primarily gastrointestinal adverse events, which contributed to the eventual suspension of further clinical development of xanomeline monotherapy.

Xanomeline–trospium (KarXT) combines xanomeline with trospium chloride, with the goal of ameliorating adverse events associated with xanomeline's activation of peripheral muscarinic receptors in peripheral tissues. Trospium is an oral, pan-muscarinic receptor antagonist that is peripherally restricted because of its inability to cross the blood–brain barrier. Trospium is approved for the treatment of overactive bladder in the USA and the EU.[18] The highly polar quaternary amine structure of trospium prevents it from entering the CNS. In a phase 1 trial in healthy volunteers (NCT02831231), KarXT demonstrated an approximately 50% lower incidence of adverse events, which were primarily gastrointestinal in nature, compared with xanomeline alone.[19] These results provide evidence that KarXT enables the administration of therapeutic doses of xanomeline with reduced adverse events. In the double-blind, phase 2 EMERGENT-1 trial (NCT03697252), 182 people with acutely exacerbated schizophrenia were randomly assigned to receive KarXT twice per day (increased to a maximum of 125 mg xanomeline and 30 mg trospium per dose) or placebo for 5 weeks.[20] The mean change from baseline to week 5 in Positive and Negative Syndrome Scale (PANSS)[21] total score was –17·4 points with KarXT and –5·9 points with placebo (least squares mean difference –11·6 points; 95% CI –16·1 to –7·1; p<0·0001; Cohen's *d* effect size 0·75). Results for secondary outcome measures, namely change in PANSS positive subscale score, PANSS negative subscale score, and PANSS Marder negative factor significantly favoured KarXT over placebo (p<0·05), except the percentage of participants with a Clinical Global Impression-Severity (CGI-S) score of 1 (normal, not ill at all) or 2 (borderline ill).[22] KarXT was generally safe and well tolerated; adverse events associated with KarXT were mild to moderate and included gastrointestinal events, including nausea, vomiting, and constipation, as well as dyspepsia and dry mouth, each of which tended to be limited to the first 1–3 weeks.[23] On the basis of the positive EMERGENT-1 trial, a phase 3 programme consisting of two inpatient trials in adults with acute exacerbation of schizophrenia using the same fundamental design as EMERGENT-1, designated the EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) trials, and two 52-week trials of long-term safety and tolerability of KarXT, designated EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309), were initiated. In addition, the ongoing ARISE (NCT05145413) trial is assessing KarXT as adjunctive therapy in people with insufficient treatment response to antipsychotic drugs. The primary objective of the EMERGENT-2 trial reported here was to evaluate the efficacy of KarXT versus placebo in reducing PANSS total score in adult inpatients with schizophrenia experiencing acute psychosis. The secondary objectives of the trial were to evaluate the reduction in PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, and CGI-S score; percentage of PANSS responders (≥30% reduction); and the safety and tolerability of KarXT compared with placebo.

See Online for appendix

## Methods

### Trial design and participants

EMERGENT-2 (NCT04659161) was a phase 3, multicentre, inpatient, randomised, double-blind, placebo-controlled trial done at 22 inpatient sites in the USA. The trial consisted of a 7-day to 14-day screening phase and a 5-week treatment period. The protocol and consent form were reviewed and approved by an independent ethics committee and central institutional review board (WCG IRB, Puyallup, WA, USA; tracking number 20203606), and the trial was conducted in compliance with the International Council for Harmonisation guidelines for current Good Clinical Practice, ethical principles of the Declaration of Helsinki, and applicable regulatory requirements.

Participants were aged 18–65 years with a primary diagnosis of schizophrenia established by comprehensive psychiatric evaluation on the basis of criteria in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition,[24] and confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders version 7.0.2.[25] Other key inclusion criteria were as follows: an acute exacerbation or relapse of psychotic symptoms requiring hospital admission with onset less than 2 months before screening; a PANSS total score of 80–120 (range 30–210; higher scores indicate more severe symptoms) with a score of 4 or higher (moderate or greater) on at least two of four symptoms (delusions, conceptual disorganisation, hallucinatory behaviour, and suspiciousness or persecution; and a CGI-S[22] scale score of 4 or higher, indicating a person who is moderately ill (range 1–7, with higher scores reflecting greater severity) at screening and baseline. Key inclusion and exclusion criteria are detailed in the appendix (pp 2–3). Informed written consent was obtained from eligible participants before the start of trial procedures.

### Randomisation and masking

Eligible participants were randomly assigned 1:1 to receive oral KarXT twice per day or placebo supplied by the sponsor as matching capsules that were identical in size, shape, colour, and appearance. Randomisation was done by the clinical research organisation VERISTAT (Southborough, MA, USA) using a computer-generated participant identification number and randomisation schedule with block randomisation, which were concealed from participants, trial personnel, and investigators. Access to the randomisation schedule was limited only to independent biometrics personnel and the authorised

pharmacy personnel or designee at each trial site. The clinical team, members of the contract research organisation, statisticians, laboratory personnel, and the sponsor were masked to treatment group assignments.

### Procedures

Oral antipsychotic medications, monoamine oxidase inhibitors, mood stabilisers, anticonvulsants, tricyclic antidepressants, selective serotonin reuptake inhibitors, or other psychoactive medications were required to have a washout period of at least five half-lives or 1 week, whichever was longer, before the baseline visit. Long-acting injectable antipsychotics were stopped at least 12 weeks (at least 24 weeks for paliperidone palmitate injection every 3 months) before baseline. Benzodiazepines for anxiety, agitation, or insomnia or sleep aids were permitted on an as-needed basis.

Baseline characteristics were ascertained on the day before randomisation and trial medication was started. The day on which trial medication was started was day 1 of the 5-week treatment period. Participants randomly assigned to the KarXT group were given doses in the first 2 days starting from 50 mg xanomeline and 20 mg trospium twice per day and then for days 3–7 100 mg xanomeline and 20 mg trospium twice per day. Beginning on day 8, there was flexible dosing with an optional dose increase to a maximum of 125 mg xanomeline and 30 mg trospium twice per day based on tolerability as assessed by the investigator, with the option to return to 100 mg xanomeline and 20 mg trospium based on tolerability if needed. The dosing regimen was identical to that of the previous phase-2 EMERGENT-1 trial.[20]

CGI-S and PANSS scores were assessed at screening, baseline, and once per week until the end of the 5-week treatment period, starting at week 1 after treatment initiation for CGI-S and at week 2 for PANSS. Adverse events were recorded at each trial visit. Orthostatic vital signs were measured supine and standing (after 2 min) at screening on the first day of treatment and at weekly visits thereafter. Vital signs were recorded 2 h after the morning dose at each visit. A resting 12-lead electrocardiogram was done at screening, on day 1, and at weeks 4 and 5. Blood to assess laboratory parameters was collected at screening and at weeks 3 and 5. The Simpson-Angus Scale (SAS),[26] Barnes Akathisia Rating Scale (BARS),[27] and Abnormal Involuntary Movement Scale (AIMS)[28] were assessed at baseline and once per week during the trial. A safety follow-up visit was done at week 6 for all participants who did not enrol in the long-term, rollover follow-up trial (EMERGENT-4).

### Outcomes

The primary efficacy endpoint was change from baseline to week 5 in PANSS total score for KarXT versus placebo.[21] There was a prespecified hierarchy of secondary outcomes for hypothesis testing of KarXT versus placebo that consisted of change from baseline to week 5 in the PANSS positive subscale score (range 7–49), PANSS negative subscale score (range 7–49),[21] PANSS Marder negative factor score (range 7–49),[29] and CGI-S scale score (range 1–7),[22] as well as the percentage of PANSS responders at week 5 (≥30% improvement from baseline in PANSS total score).

Safety was assessed through adverse event (defined using preferred terms of Medical Dictionary for Regulatory Activities version 23.1) monitoring and by measuring vital signs and weight, clinical laboratory evaluations, and electrocardiogram parameters. Treatment-emergent adverse events (TEAEs) were rated for severity. The SAS assessed extrapyramidal motor symptoms (range 0–40; higher scores indicating greater parkinsonian symptoms), the BARS assessed akathisia (range 0–14; higher scores indicating greater symptoms of akathisia), and AIMS was used to assess dyskinesia (range 0–28; rating ≥2 indicating dyskinesia). The trial included pharmacokinetic and exploratory endpoints that are not reported here.

### Statistical analysis

Statistical analyses were done using SAS statistical analysis software version 9.4.[30]

Assuming a PANSS total score difference of 8 points in the change from baseline to week 5 between KarXT and placebo and an SD of 16 on the basis of results from EMERGENT-1 and other similar antipsychotic registration trials, a sample size of approximately 172 participants (86 evaluable participants per group) was calculated to result in a power of 90·3% for a two-sided test at a significance level of 0·05. With an estimated dropout rate of 30%, a total of 246 participants were estimated to be enrolled.

Baseline demographics and characteristics for the intent-to-treat (ITT) population were summarised by the number and percentage of participants for sex and race and mean scores with SDs were calculated for baseline age, BMI, PANSS score, and CGI-S score by treatment group and for the overall population. Baseline demographics and characteristics for the ITT, modified ITT (mITT), and safety populations were compared.

Efficacy analyses were done using the mITT population, which included all randomly assigned participants who received at least one dose of KarXT or placebo and had a baseline and at least one post-baseline PANSS assessment. The primary efficacy endpoint was analysed using a mixed model for repeated measures (MMRM). Least squares mean change from baseline, SE, and least squares mean difference between the KarXT and placebo groups at week 5 along with the 95% CI and a two-sided p value were calculated for the primary endpoint. A two-sided p value of ≤0·05 was considered statistically significant.

Analyses accounted for multiplicity by using a fixed-sequence testing procedure.[31] If the primary efficacy endpoint was significantly different between the KarXT and placebo groups at a two-sided significance level

of 0·05, then prespecified secondary outcome measures were tested using hierarchical hypothesis tests in a fixed-sequence procedure in the following order: PANSS positive subscale; PANSS negative subscale; PANSS Marder negative factor; CGI-S; and percentage of PANSS responders (≥30% improvement in PANSS total score) at week 5. In addition, other PANSS response thresholds of ≥20%, ≥40%, and ≥50% were assessed. A PANSS total score reduction of ≥20% is a standard measure of the minimal clinically meaningful change and a score reduction of ≥50% represents much better.[32] The continuous-variable primary endpoint and secondary outcome measures were analysed using an MMRM. Missing data were not explicitly imputed but were handled by the MMRM. The least squares mean change from baseline, SE, and least squares mean difference between the KarXT and placebo groups at week 5, along with the 95% CI and a two-sided p value were calculated for PANSS negative subscale, PANSS positive subscale, and PANSS Marder negative factor secondary outcomes measures. The responder rates (in percentages) for the KarXT and placebo groups, the difference of responder rates between the two treatment groups, and 95% CI and two-sided p values were calculated.

A Cohen's *d* effect size was calculated for the primary efficacy endpoint and secondary outcome measures using the absolute value of the difference in least squares change in score from baseline at week 5 between the KarXT and placebo groups divided by the pooled SD of the change.

For the PANSS responder analysis, PANSS items were rescaled from a range of 1–7 to 0–6 or, equivalently, PANSS total scores were floor-adjusted by subtracting 30 points from baseline and post-baseline scores.[33] The percentage of PANSS responders at each week was calculated and summarised by treatment group and visit. The percentage of PANSS responders at week 5 was compared between treatment groups (KarXT and placebo) using the Cochran-Mantel-Haenszel test.

Safety analyses were done on all randomly assigned participants who received at least one dose of KarXT or placebo (safety population). All safety and tolerability data were summarised descriptively by treatment group and timepoint as appropriate. The number and percentage of participants with any TEAEs, any serious TEAE, any severe TEAE, and any TEAE leading to trial drug discontinuation were summarised by treatment group. Mean change (SD) from baseline to week 5 was calculated for measures of body weight, prolactin, and vital signs, and the SAS, BARS, and AIMS scores, and summarised by treatment group.

## Role of the funding source

Karuna Therapeutics designed the protocol and provided the trial drug and placebo; the funder had no role in data collection. The contract research organisation Syneos

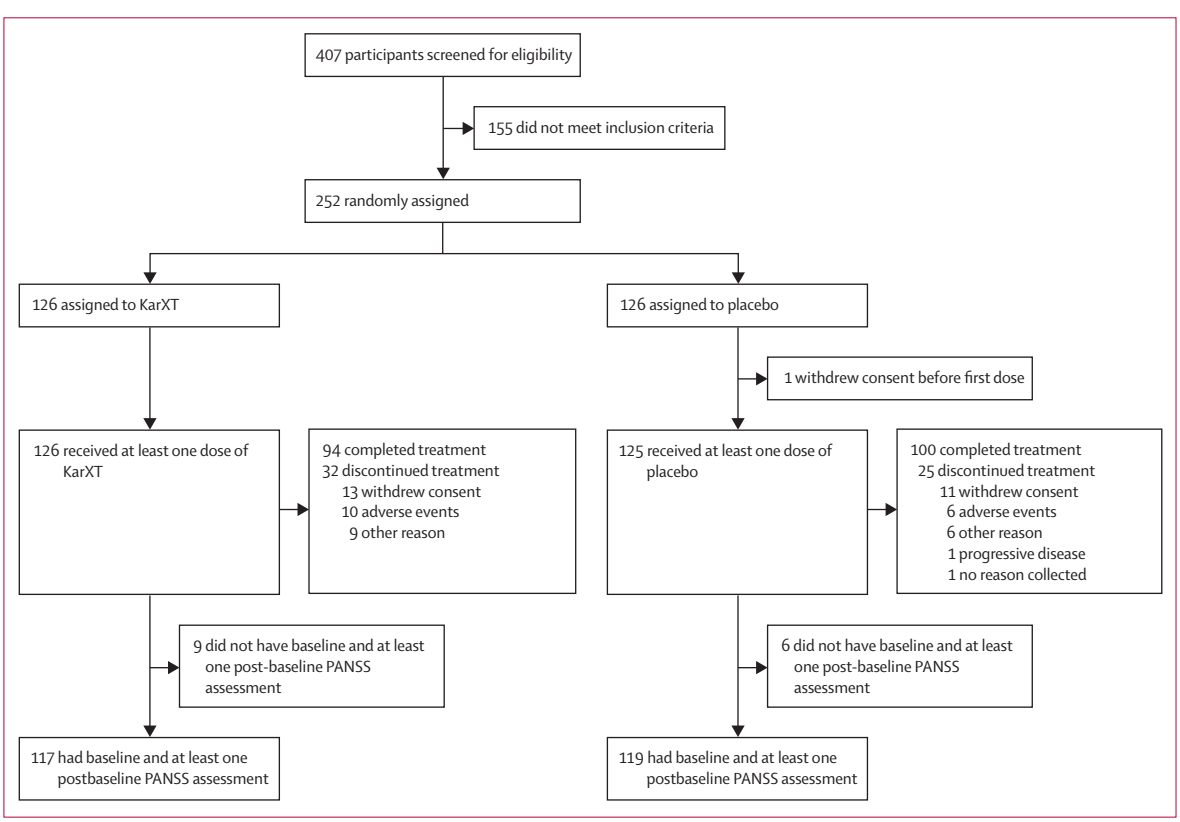


***Figure 1:*** **Trial profile**
ITT=intent-to-treat. KarXT=xanomeline–trospium. mITT=modified intent-to-treat. PANSS=Positive and Negative Syndrome Scale.

| | ITT population | | | mITT population | | |
|---|---|---|---|---|---|---|
| | KarXT (n=126) | Placebo (n=126) | Total (n=252) | KarXT (n=117) | Placebo (n=119) | Total (n=236) |
| Age, years | 45·6 (10·4) | 46·2 (10·8) | 45·9 (10·6) | 45·9 (10·4) | 46·1 (10·8) | 46·0 (10·6) |
| Sex | | | | | | |
| Male | 95 (75%) | 95 (75%) | 190 (75%) | 87 (74%) | 91 (77%) | 178 (75%) |
| Female | 31 (25%) | 31 (25%) | 62 (25%) | 30 (26%) | 28 (23%) | 58 (25%) |
| Race | | | | | | |
| Asian | 2 (2%) | 1 (1%) | 3 (1%) | 2 (2%) | 0 (0%) | 2 (1%) |
| Black or African American | 97 (77%) | 92 (73%) | 189 (75%) | 91 (78%) | 86 (72%) | 177 (75%) |
| White | 26 (21%) | 31 (25%) | 57 (23%) | 23 (20%) | 31 (26%) | 54 (23%) |
| Other | 1 (1%) | 2 (2%) | 3 (1%) | 1 (1%) | 2 (2%) | 3 (1%) |
| BMI, kg/m$^2$ | 30·2 (5·4) | 29·1 (5·4) | 29·6 (5·4) | 30·1 (5·5) | 29·1 (5·4) | 29·6 (5·5) |
| PANSS score | | | | | | |
| Total score | 98·3 (8·9) | 97·9 (9·7) | 98·1 (9·3) | 98·2 (8·9) | 97·7 (9·4) | 98·0 (9·1) |
| Positive subscale score | 26·8 (3·7) | 26·7 (4·0) | 26·7 (3·9) | 26·8 (3·8) | 26·5 (3·7) | 26·7 (3·8) |
| Negative subscale score | 22·9 (4·0) | 22·9 (3·8) | 22·9 (3·9) | 22·9 (4·1) | 22·9 (3·9) | 22·9 (4·0) |
| Marder negative factor score | 22·9 (5·0) | 22·5 (4·7) | 22·7 (4·9) | 22·8 (5·1) | 22·5 (4·7) | 22·7 (4·9) |
| CGI-S score | 5·1 (0·6) | 5·1 (0·6) | 5·1 (0·6) | 5·1 (0·6) | 5·1 (0·6) | 5·1 (0·6) |

Data were mean (SD) or n (%). CGI-S=Clinical Global Improvement-Severity. ITT=intent to treat. mITT=modified intent to treat. PANSS=Positive and Negative Syndrome Scale.

***Table 1:*** **Baseline patient demographics and characteristics**

Health (Morrisville, NC, USA) was responsible for overall trial conduct, and VERISTAT (Southborough, MA, USA) did all data analyses. Representatives from Karuna Therapeutics were involved in interpreting the data and preparing the manuscript. All of the authors are employees of or consultants to Karuna Therapeutics.

## Results

407 people at 22 inpatient sites in the USA were screened between Dec 16, 2020, and April 13, 2022, of which 252 participants meeting the enrolment criteria were randomly assigned (1:1) to KarXT (n=126) or placebo (n=126; figure 1). Among the 155 people ineligible for participation, 65% had abnormal laboratory values or physical examination findings, 30% were not included in the study because their medical or psychiatric history did not meet the trial eligibility criteria, and the remaining 5% had several other reasons. The percentage of screened participants excluded was similar across trial sites. The safety population included 251 participants (KarXT n=126; placebo n=125), who received at least one dose of trial medication. The mITT population included 236 participants (KarXT n=117; placebo n=119), who received at least one PANSS assessment after randomisation. 32 (25%) participants in the KarXT group and 26 (21%) participants in the placebo group terminated the trial early. The most common reasons for discontinuing the trial early were withdrawn consent and adverse events, including three participants in the KarXT group and six participants in the placebo group who discontinued because of a psychiatric disorder. There were no deaths.

No meaningful differences in baseline demographic and clinical characteristics were observed between treatment groups (table 1) and baseline characteristics were similar between the mITT, ITT, and safety populations. Mean baseline PANSS total score was 98·3 points (SD 8·9) in the KarXT group and 97·9 points (9·7) in the placebo group. 104 (94%) of 111 participants in the KarXT group reached the highest trial drug dose (125 mg/30 mg twice per day) compared with 123 (98%) of 125 participants in the placebo group; seven (6%) participants in the KarXT group and no participants in the placebo group had a single per-protocol reduction to a lower dose for tolerability reasons. 119 (94%) participants in the KarXT group and 116 (93%) participants in the placebo group had taken at least one psychoactive medication in the previous 6 months. Previous medication use was generally similar between treatment groups. The most common previous medications in the two groups included lorazepam (42 [33%] in the KarXT group *vs* 37 [30%] in the placebo group), zolpidem (40 [32%] *vs* 41 [33%]), risperidone (28 [22%] *vs* 27 [22%]), and quetiapine (28 [22%] *vs* 35 [28%]).

For the primary endpoint, the KarXT group demonstrated a statistically significant 9·6-point greater reduction (95% CI –13·9 to –5·2) in PANSS total score at week 5 than the placebo group (table 2; figure 2A). A predefined sensitivity analysis of PANSS total score change from baseline for completers was consistent with the primary analysis (appendix p 4).

Compared with placebo at week 5, KarXT demonstrated a 2·9-point reduction (95% CI –4·3 to –1·5) in PANSS positive-subscale score (table 2; figure 2B), a 1·8-point reduction (95% CI –3·1 to –0·5) in PANSS negative-subscale score (table 2; figure 2C), and a 2·2-point reduction (95% CI –3·6 to –0·8) in PANSS Marder negative factor score (table 2; figure 2D). For CGI-S scale

| | KarXT (n=117) | Placebo (n=119) | Difference (95% CI) | Cohen's *d* | p value |
|---|---|---|---|---|---|
| **Primary endpoint** | | | | | |
| PANSS total score* | –21·2 (1·7) | –11·6 (1·6) | –9·6 (–13·9 to –5·2) | 0·61 | <0·0001 |
| **Secondary outcome measures** | | | | | |
| PANSS positive symptom subscale score† | –6·8 (0·5) | –3·9 (0·5) | –2·9 (–4·3 to –1·5) | 0·59 | <0·0001 |
| PANSS negative symptom subscale score‡ | –3·4 (0·5) | –1·6 (0·5) | –1·8 (–3·1 to –0·5) | 0·40 | 0·0055 |
| PANSS Marder negative factor score§ | –4·2 (0·5) | –2·0 (0·5) | –2·2 (–3·6 to –0·8) | 0·44 | 0·0022 |
| CGI-S scale score¶ | –1·2 (0·1) | –0·7 (0·1) | –0·6 (–0·9 to –0·3) | 0·58 | <0·0001 |
| PANSS responders (≥30% reduction from baseline in PANSS total score)‖ | 51/93 (55%) | 28/99 (28%) | 27% (13 to 39) | NA | <0·0001 |

Data are LSM change (SE) from baseline or n/N (%). CGI-S=Clinical Global Impression–Severity. mITT=modified intent-to-treat. NA=not applicable. PANSS=Positive and Negative Syndrome Scale. KarXT=xanomeline–trospium. *PANSS total score range, 30–120 (higher score reflects greater severity). †PANSS positive symptoms subscale score range, 7–49 (higher score reflects greater severity). ‡PANSS negative symptoms subscale score range, 7–49 (higher score reflects greater severity). §PANSS Marder negative factor range, 7–49 (higher score reflects greater severity). ¶CGI-S scale range, 1–7 (1 indicating no illness and 7 indicating severe illness). ‖On the basis of the floor-adjusted total score (total score minus 30), assessed in patients with available week-5 scores.

***Table 2:*** **Efficacy measures at week 5 (mITT population)**

scores, least squares mean change from baseline to week 5 was –1·2 points (SE 0·1) in the KarXT group versus –0·7 points (0·1) in the placebo group (table 2, figure 3). Finally, 51 (55%) of 93 participants in the KarXT group compared with 28 (28%) of 99 participants in the placebo group had a ≥30% improvement from baseline to week 5 in PANSS total score (rate difference 27%; 95% CI 13 to 39; p<0·0001; table 2; figure 4). A higher proportion of participants in the KarXT group than the placebo group had a ≥20% (60 [65%] of 93 *vs* 36 [36%] of 99; rate difference 28%; 95% CI 14 to 41; p<0·0001), ≥40% (36 [39%] of 93 *vs* 21 [21%] of 99; rate difference 18%; 5 to 30; p=0·0068), and ≥50% (19 [20%] of 93 *vs* 12 [12%] of 99; rate difference 8%; –2 to 19; p=0·18) improvement from baseline to week 5 in PANSS total score.

At least one TEAE was experienced by 95 (75%) participants in the KarXT group versus 73 (58%) participants in the placebo group (table 3). TEAEs occurring in ≥5% of participants in the KarXT group were generally gastrointestinal in nature. The most common TEAEs (≥5%) reported in the KarXT group, and at a rate at least twice that observed in the placebo group were constipation, dyspepsia, nausea, vomiting, hypertension, dizziness, and gastro-oesophageal reflux disease. Vomiting was intermittent and generally mild, with about a third of vomiting TEAEs consisting of only a single episode of emesis. The rates of serious or severe TEAEs were low and similar between treatment groups. Four serious TEAEs occurred (KarXT, suicidal ideation, n=2; placebo, appendicitis, n=1, and worsening of schizophrenia, n=1), none of which were determined by the investigator to be drug related. Rates of discontinuation related to TEAEs were similar between KarXT (nine [7%]) and placebo (seven [6%]). Adverse events of special interest have been summarised (appendix p 5).

Two participants in the KarXT group and one participant in the placebo group had elevations in hepatic transaminases. None of these participants had an elevation of greater than five times the upper limit of normal, and none of the participants had elevated bilirubin concentrations or met the criteria for Hy's Law.

KarXT was not associated with weight gain compared with placebo. The mean change in bodyweight from baseline to week 5 was 1·4 kg (SD 3·31) in the KarXT group and 2·5 kg (6·92) in the placebo group (table 3). Of the 94 individuals in the KarXT group and 100 individuals in the placebo group for whom weight data were available at week 5, no participants in the KarXT group and one (1%) participant in the placebo group reported a TEAE of increased weight. The number of participants who experienced a ≥7% increase in weight from baseline to week 5 was six (6%) in the KarXT group and 13 (13%) in the placebo group. The mean change in BMI from baseline to week 5 was 0·5 kg/m² (SD 1·09) in the KarXT group and 0·8 kg/m² (2·17) in the placebo group. KarXT was not associated with greater changes than placebo in metabolic parameters (appendix p 6).

The incidences of extrapyramidal motor symptoms or akathisia reported were low and similar between treatment groups. No participants in either treatment group reported a TEAE of extrapyramidal disorder. Only one (1%) participant in each treatment group reported symptoms classified by the site investigator as akathisia; both cases resolved during the trial without changes in trial drug administration. In addition, the mean change from baseline to week 5 in BARS score in the KarXT group was –0·1 points (SD 1·09) versus –0·2 points (0·98) in the placebo group, and mean change in SAS score was 0 points (0·61) in the KarXT group versus –0·1 points (0·70) in the placebo group (table 3). No cases of dyskinesia were reported in either treatment group; mean change in AIMS score was 0 (SD 0·28) in the KarXT group and 0 (0·10) in the placebo group. No participants in the KarXT group and one (1%) participant in the placebo group were administered the anti-parkinsonism medication benzatropine.

Mean blood pressure measures were similar between KarXT and placebo at each timepoint during the trial as

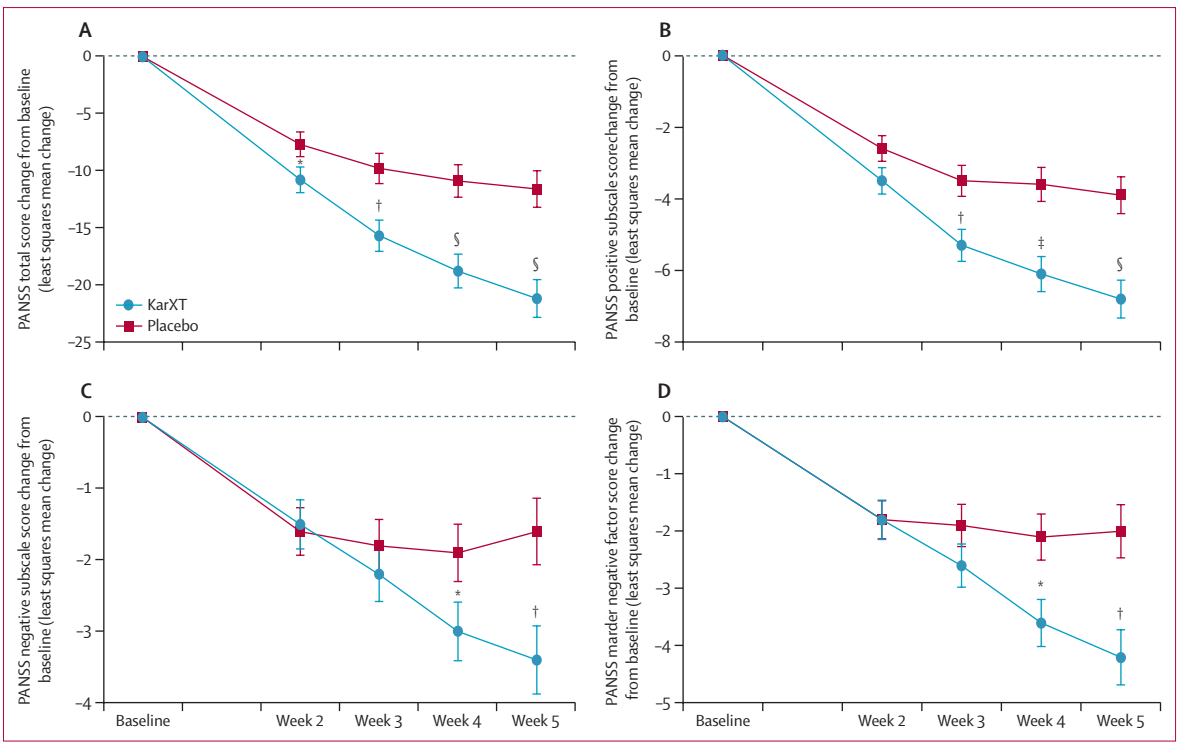


***Figure 2:*** **Mean change from baseline in PANSS total score (A), PANSS positive subscale score (B), PANSS negative subscale score (C), and PANSS Marder negative factor score (D)**
Error bars indicate SEM. KarXT=xanomeline–trospium. PANSS=Positive and Negative Syndrome Scale. *p<0·05. †p<0·01. ‡p<0·001. §p<0·0001.

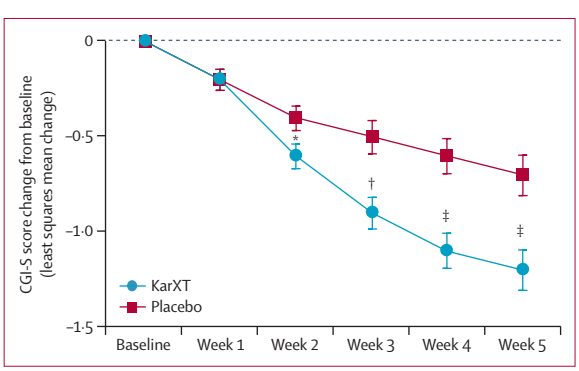


***Figure 3:*** **Mean change from baseline in CGI-S score**
Error bars indicate SEM. Least squares mean changes for KarXT and placebo were estimated using mixed-model repeated measures. CGI-S=Clinical Global Impression–Severity. KarXT=xanomeline–trospium. *p<0·05. †p<0·001. ‡p<0·0001.

measured 2 h after dose, corresponding to the time of maximum plasma concentration of KarXT. Mild nominal increases in systolic and diastolic blood pressure (2–3 mmHg) in the KarXT group were observed at peak drug concentrations during the first week of KarXT treatment and partially attenuated as treatment continued; after the first week, mean blood pressure measures were generally similar between treatment groups. TEAEs of hypertension (MedDRA preferred term; not necessarily reflective of clinical hypertension) were largely transient excursions of blood pressure and most resolved during the trial. In the subset of patients with a recorded TEAE of increased blood pressure, mean blood pressure at endpoint was similar to baseline measures and did not lead to trial discontinuation. One participant in each of the KarXT and placebo groups had an increase in supine systolic blood pressure of at least 15 mmHg or diastolic blood pressure of at least 10 mm Hg at day 35. KarXT treatment was associated with an increase from baseline in supine heart rate compared with placebo that peaked at day 8 (mean 14·3 beats per minute [bpm], SD 13·87, *vs* 3·6 bpm, 12·09) and decreased slightly through day 28 (mean 11·6 bpm, SD 13·86, *vs* 2·4 bpm, 12·75). No syncopal events were observed. Finally, KarXT was not associated with greater changes than placebo in the corrected QT interval (appendix p 6).

## Discussion

In this phase 3 clinical trial, treatment of adults with schizophrenia with acute psychosis with the dual $M_1$ and $M_4$ receptor preferring muscarinic agonist KarXT was associated with significant improvements in positive and negative symptoms compared with placebo over the 5-week treatment period. Although demographics in international trials might be more representative, the baseline demographics and clinical characteristics including age, sex, race, BMI, and symptom severity of

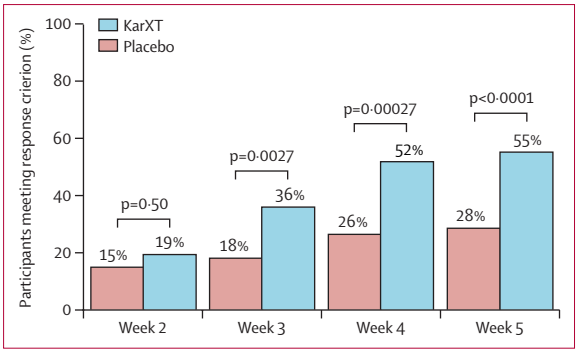


***Figure 4:*** **Percentage of participants with ≥30% reduction from baseline in PANSS total score by trial week**
Based on floor-adjusted total score (total score minus 30). PANSS=Positive and Negative Syndrome Scale. KarXT=xanomeline–trospium.

| | KarXT (n=126) | Placebo (n=125) |
|---|---|---|
| Any TEAE | 95 (75%) | 73 (58%) |
| Serious TEAE | 2 (2%) | 2 (2%) |
| Severe TEAE | 2 (2%) | 4 (3%) |
| TEAE leading to discontinuation | 9 (7%) | 7 (6%) |
| TEAE occurring in ≥5% of participants in the KarXT group | | |
| Constipation | 27 (21%) | 13 (10%) |
| Dyspepsia | 24 (19%) | 10 (8%) |
| Headache | 17 (14%) | 15 (12%) |
| Nausea | 24 (19%) | 7 (6%) |
| Vomiting | 18 (14%) | 1 (1%) |
| Hypertension | 12 (10%) | 1 (1%) |
| Dizziness | 11 (9%) | 4 (3%) |
| Gastro-oesophageal reflux disease | 8 (6%) | 0 |
| Diarrhoea | 7 (6%) | 4 (3%) |
| Change from baseline to week 5* | | |
| Body weight, kg | 1·4 (3·31) | 2·5 (6·92) |
| Prolactin, mg/L | 1·0 (9·27) | 0·8 (9·59) |
| Simpson-Angus Scale score | 0 (0·61) | –0·1 (0·70) |
| Barnes Akathisia Rating Scale score | –0·1 (1·09) | –0·2 (0·98) |
| Abnormal Involuntary Movement Scale score | 0·0 (0·28) | 0·0 (0·10) |

Data are n (%) or mean (SD). TEAE=treatment-emergent adverse event. KarXT=xanomeline–trospium. *Number of participants in the KarXT and placebo groups for which data were available at week 5: for body weight in KarXT, n=94, and in placebo, n=100; for prolactin in KarXT, n=75, and in placebo, n=85; for the Simpson-Angus Scale in KarXT, n=92, and in placebo, n=99; for the Barnes Akathisia Rating Scale in KarXT, n=92, and in placebo, n=99; and for the Abnormal Involuntary Movement Scale in KarXT, n=92, and in placebo, n=99.

***Table 3:*** **TEAEs and safety during the 5-week treatment period (safety population)**

the EMERGENT-2 population were broadly consistent with those of clinical trials in schizophrenia done over the past decade in the USA, including in EMERGENT-1.[20] On the primary endpoint, KarXT treatment showed a significant 9·6-point difference in mean change from baseline to week 5 in PANSS total score compared with placebo (p<0·0001) with an effect size of 0·61. Combining this result with the effect size observed in the EMERGENT-1 trial (0·75) suggests the potential for KarXT to be an efficacious treatment with a unique pharmacology for people with schizophrenia. The KarXT group showed significant improvements (all p<0·05) compared with placebo at week 5 on the PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, and CGI-S scores. The percentage of participants reaching the prespecified PANSS responder criteria of ≥30% reduction from baseline in PANSS total score at week 5 was significantly greater with KarXT than placebo (p<0·0001).

KarXT was generally well tolerated, with a side-effect profile substantially consistent with that observed in EMERGENT-1.[20] The overall percentage of participants who discontinued treatment was similar between the KarXT and placebo groups (25% *vs* 21%), as was the percentage of people discontinuing because of TEAEs (KarXT, nine [7%] of 126; placebo, seven [6%] of 125). The most common TEAEs associated with KarXT were constipation, dyspepsia, nausea, vomiting, hypertension, dizziness, and gastro-oesophageal reflux disease, which reflect the activity of xanomeline and of trospium at muscarinic receptors. The majority of TEAEs occurred within the first 2–3 weeks, were transient, and resolved before the end of the trial. Other trials of xanomeline alone for 6 months[16] or trospium alone for 9 months,[35] albeit in different patient populations, do not suggest the emergence of new safety or tolerability issues with longer treatment, but results from two ongoing 52-week trials of KarXT will better characterise the long-term safety and tolerability profile of KarXT in people with schizophrenia.

KarXT was not associated with common problematic adverse events of currently available antipsychotic medications, such as extrapyramidal motor symptoms or akathisia, weight gain, metabolic changes, prolactin elevation, or somnolence. Measures of extrapyramidal motor symptoms or akathisia were similar in both the KarXT and placebo groups and showed no significant changes from baseline to week 5. There were no discontinuations because of extrapyramidal motor symptoms, nor was any pharmacological treatment of adverse events initiated. Adverse events associated with KarXT treatment were primarily gastrointestinal in nature, consistent with previous trials and the expression of muscarinic receptors in the gastrointestinal tract.[14] Rates of the most common adverse events in the KarXT group (constipation, dyspepsia, nausea, and vomiting) generally decreased over the course of the trial.

TEAE rates of hypertension were greater in the KarXT (n=12, 10%) versus placebo group (n=1, 1%). However, mean changes in systolic and diastolic blood pressure assessed 2 h after dose (at the time of maximum plasma concentration) were similar between the KarXT and placebo treatment groups and remained relatively flat over

the course of the 5-week trial, implying that hypertension TEAEs were mostly mild transient elevations of blood pressure in a small number of patients. An ongoing ambulatory blood pressure monitoring trial in people with schizophrenia will provide more insight into any effect on blood pressure. As in previous trials, an increase in supine heart rate in the first week of treatment that decreased in magnitude by the end of the trial was observed in the KarXT group compared with the placebo group.

The efficacy and safety results from this phase 3 trial were similar to those reported for the phase 2 EMERGENT-1 trial.[20] Similarities between the trials include a flexible dose design with two groups (KarXT and placebo), a 5-week treatment duration in an inpatient setting, and similar inclusion and exclusion criteria. The placebo response on the primary outcome (PANSS total score least squares mean change from baseline at week 5) was higher in EMERGENT-2 (–11·6 points) than EMERGENT-1 (–5·9 points)[20] and higher than the mean placebo response (–6·25 points) reported in a meta-regression analysis of 167 randomised, double-blind, placebo-controlled registration trials of antipsychotic drugs in schizophrenia.[34,36,37] The higher placebo response in the phase 3 trial might relate to the larger number of investigational sites[36] and greater expectation bias following the reported efficacy of KarXT in the phase 2 EMERGENT-1 trial.

Consistent with the EMERGENT-1 trial, EMERGENT-2 demonstrated statistically significant improvement in negative symptoms with KarXT compared with placebo based on changes from baseline to week 5 in PANSS negative subscale score (1·8-point reduction *vs* placebo) and PANSS Marder negative factor score (2·2-point reduction *vs* placebo). Together, these results support further testing of KarXT as a treatment for primary negative symptoms in an appropriately designed study in people with persistent negative symptoms, as the Marder negative factor might be less susceptible to influence by improvement in positive symptoms than the PANSS negative subscale.[38] However, caution is warranted in interpreting these results given the acute nature of the trial and potential pseudospecific effects related to significant improvements in positive symptoms. Longer-term studies in people with stable positive symptoms and predominantly negative symptoms are needed to characterise the effects of KarXT on enduring primary negative symptoms.

The trial had limitations typical for antipsychotic registration trials in patients with schizophrenia and an acute exacerbation of psychosis. The duration of this trial was 5 weeks and did not assess durability of effect or long-term safety of KarXT treatment for what is a lifelong illness. However, a relatively rapid improvement in psychotic symptoms (2 weeks) was observed and the superiority of KarXT versus placebo continued to increase through week 5, suggesting that a greater effect size might occur at later time points. Trials with longer-term follow-ups are warranted, and two 52-week trials are underway (NCT04659174 and NCT04820309). Further, the trial did not include an active control group, which would allow for more direct comparison of KarXT with other antipsychotic drugs.

In conclusion, KarXT demonstrated efficacy and safety and was generally well tolerated in the phase 3 EMERGENT-2 trial in adults with schizophrenia with acute psychosis treated over 5 weeks. KarXT resulted in significantly greater improvements than placebo across the primary endpoint and all secondary outcome measures, which assessed overall symptoms as well as positive and negative symptoms and symptomatic response status. KarXT showed a distinctive safety and tolerability profile and was not associated with many of the adverse events typically observed with currently approved antipsychotic drugs, such as extrapyramidal motor symptoms or akathisia, weight gain, metabolic changes, prolactin elevations, or somnolence. Treatment with KarXT resulted in predominantly gastrointestinal side-effects, which were mild to moderate in severity and generally transient. These results confirm those from the EMERGENT-1 trial and represent the second positive pivotal trial with KarXT in people with acutely exacerbated schizophrenia. The antipsychotic properties of KarXT are mediated through $M_1$ and $M_4$ muscarinic receptors and KarXT is devoid of direct $D_2$ dopamine receptor-blocking activity. Because of this unique pharmacology and clinical profile, KarXT has the potential to be the first in a new class of antipsychotic medications since the launch of second-generation antipsychotic drugs more than 30 years ago. The EMERGENT-3 trial (identical design to EMERGENT-2), two open-label trials of up to 52 weeks in duration (EMERGENT-4 and EMERGENT-5), and a trial of KarXT as adjunctive therapy (ARISE) in people with insufficient treatment response to antipsychotic drugs are ongoing to further establish the efficacy and safety of KarXT in the treatment of psychosis in people with schizophrenia.

#### Contributors

SS, IK, AB, and SKB conceptualised the trial and contributed to its design. SS, IK, RK, and SKB were involved in the implementation of the trial. HZ oversaw the statistical analyses. All authors were involved in the interpretation of the results, reviewed and commented on the paper, had full access to all of the trial data, take responsibility for the data integrity and the accuracy of the analyses, and were responsible for the decision to submit the manuscript. IK, SS, and HZ verified the data.

#### Declaration of interests

CUC has been a consultant, advisor, or both consultant and advisor to or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo Pharma, Biogen, Boehringer Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, Intra-Cellular Therapies, Janssen or Johnson & Johnson, Karuna Therapeutics, LB Pharma, Lundbeck, MedAvante-ProPhase, MedinCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine Biosciences, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, 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 Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, ROVI, Sage, Supernus, Tolmar, 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, Mindpax, PsiloSterics, and Quantic. AB

has been a consultant, advisor, or both consultant and advisor for Arrivo Sirtsei, BioXcel, Karuna Therapeutics, Neumarker, and Perception Neuroscience, and holds equity in Karuna Therapeutics and Perception Neuroscience. SMP is an employee of Karuna Therapeutics, is in a leadership or fiduciary role at Karuna Therapeutics, Sage Therapeutics, and Voyager Therapeutics, and holds equity in Eli Lilly Pharmaceuticals, Karuna Therapeutics, Sage Therapeutics, and Voyager Therapeutics. IK, SS, HZ, ACM, and SKB are employees of and hold equity in Karuna Therapeutics. RK was a principal investigator for the EMERGENT-2 study.

#### Data sharing

Data will be made available from the corresponding author on reasonable request, subject to review.

#### Acknowledgments

The EMERGENT-2 trial was sponsored by Karuna Therapeutics. The authors thank Matthew Jacobson, Adrienne Drinkwater, Paula Stuckart, and Kimberly Church of Apollo Medical Communications for medical writing and editorial assistance, which was funded by Karuna Therapeutics.

#### References

1 Marder SR, Cannon TD. Schizophrenia. *N Engl J Med* 2019; **381:** 1753–61.
2 Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. *Lancet* 2022; **399:** 473–86.
3 GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396:** 1204–22.
4 GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 2022; **9:** 137–50.
5 Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry* 2005; **62:** 247–53.
6 Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. *JAMA Psychiatry* 2015; **72:** 1172–81.
7 Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry* 2017; **4:** 295–301.
8 Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol* 2010; **24** (4 suppl)**:** 81–90.
9 Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019; **394:** 939–51.
10 Lobo MC, Whitehurst TS, Kaar SJ, Howes OD. New and emerging treatments for schizophrenia: a narrative review of their pharmacology, efficacy and side effect profile relative to established antipsychotics. *Neurosci Biobehav Rev* 2022; **132:** 324–61.
11 Kane JM, Agid O, Baldwin ML, et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. *J Clin Psychiatry* 2019; **80:** 18com12123.
12 Siskind D, Orr S, Sinha S, et al. Rates of treatment-resistant schizophrenia from first-episode cohorts: systematic review and meta-analysis. *Br J Psychiatry* 2022; **220:** 115–20.
13 Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry* 2002; **63:** 892–909.
14 Paul SM, Yohn SE, Popiolek M, Miller AC, Felder CC. Muscarinic acetylcholine receptor agonists as novel treatments for schizophrenia. *Am J Psychiatry* 2022; **179:** 611–27.
15 Shannon HE, Bymaster FP, Calligaro DO, et al. Xanomeline: a novel muscarinic receptor agonist with functional selectivity for M1 receptors. *J Pharmacol Exp Ther* 1994; **269:** 271–81.
16 Bodick NC, Offen WW, Levey AI, et al. Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol* 1997; **54:** 465–73.
17 Shekhar A, Potter WZ, Lightfoot J, et al. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatry* 2008; **165:** 1033–39.
18 Staskin D, Kay G, Tannenbaum C, et al. Trospium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder. *Int J Clin Pract* 2010; **64:** 1294–300.
19 Breier A, Brannan SK, Paul SM, Miller AC. Evidence of trospium's ability to mitigate cholinergic adverse events related to xanomeline: phase 1 study results. *Psychopharmacology* 2023; **240:** 1191–98.
20 Brannan SK, Sawchak S, Miller AC, Lieberman JA, Paul SM, Breier A. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. *N Engl J Med* 2021; **384:** 717–26.
21 Kay SR, Opler LA, Lindenmayer JP. The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br J Psychiatry Suppl* 1989; **7:** 59-67.
22 Haro JM, Kamath SA, Ochoa S, et al. The clinical global impression-schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. *Acta Psychiatr Scand Suppl* 2003; **416**: 16–23.
23 Correll CU, Angelov AS, Miller AC, Weiden PJ, Brannan SK. Safety and tolerability of KarXT (xanomeline-trospium) in a phase 2, randomized, double-blind, placebo-controlled study in patients with schizophrenia. *Schizophrenia* 2022; **8:** 109.
24 American Psychiatric Association D. S. M. Task Force. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Arlington, VA: American Psychiatric Association, 2013.
25 Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59** (suppl 20)**:** 22–33.
26 Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970; **212:** 11–19.
27 Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989; **154:** 672–76.
28 Guy W. ECDEU Assessment manual for psychopharmacology. Revised. Rockville, MD: National Institute of Mental Health, 1976.
29 Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry* 1997; **58:** 538–46.
30 SAS Institute. SAS/ACCESS® 9.4 interface to ADABAS: reference. Cary, NC: SAS Institute, 2013.
31 Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J Stat Planning Inference* 2001; **99:** 25–40.
32 Leucht S. Measurements of response, remission, and recovery in schizophrenia and examples for their clinical application. *J Clin Psychiatry* 2014; **75** (suppl 1)**:** 8–14.
33 Leucht S, Davis JM, Engel RR, Kane JM, Wagenpfeil S. Defining 'response' in antipsychotic drug trials: recommendations for the use of scale-derived cutoffs. *Neuropsychopharmacology* 2007; **32:** 1903–10.
34 Leucht S, Leucht C, Huhn M, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. *Am J Psychiatry* 2017; **174:** 927–42.
35 Zinner NR, Dmochowski RR, Staskin DR, Siami PF, Sand PK, Oefelein MG. Once-daily trospium chloride 60 mg extended-release provides effective, long-term relief of overactive bladder syndrome symptoms. *Neurourol Urodyn* 2011; **30:** 1214–19.
36 Leucht S, Chaimani A, Leucht C, et al. 60 years of placebo-controlled antipsychotic drug trials in acute schizophrenia: meta-regression of predictors of placebo response. *Schizophr Res* 2018; **201:** 315–23.
37 Krause M, Huhn M, Schneider-Thoma J, Bighelli I, Gutsmiedl K, Leucht S. Efficacy, acceptability and tolerability of antipsychotics in patients with schizophrenia and comorbid substance use. A systematic review and meta-analysis. *Eur Neuropsychopharmacol* 2019; **29:** 32–45.
38 Weiden PJ, Breier A, Kavanagh S, Miller AC, Brannan SK, Paul SM. Antipsychotic efficacy of KarXT (xanomeline-trospium): post hoc analysis of positive and negative syndrome scale categorical response rates, time course of response, and symptom domains of response in a phase 2 study. *J Clin Psychiatry* 2022; **83:** 21m14316.