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A combination of xanomeline with trospium as an innovative pharmacological strategy for schizophrenia

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Summary

Treating schizophrenia involves many difficulties. It is estimated that around 20–33% of patients do not respond to the proposed therapy with available antipsychotic drugs, which is associated with the occurrence of problems with everyday functioning. Currently used drugs are mainly characterized by regulation of the dopaminergic system. This review compiles information on the effectiveness of a complex drug (xanomeline with trospium) for schizophrenia with a new mechanism of action. The drug, known as KarXT, targets proteins in the brain known as muscarinic receptors. Activation of these receptors suppresses the release of the neurotransmitter dopamine, whose deficiency is associated with the occurrence of key symptoms of schizophrenia, such as hallucinations and delusions. The drug offers hope for better efficacy in treating schizophrenia and better tolerability than current therapies. On September 27, 2024, the FDA approved Cobenfy (known as KarXT – xanomeline with trospium), a new oral medication for adults with schizophrenia. The approval of Cobenfy is a landmark moment in the treatment of schizophrenia because it offers a new, innovative treatment option for this challenging condition.

Key words: schizophrenia, xanomeline, KarXT

Introduction

Treatment of schizophrenia is fraught with many difficulties. It is estimated that approximately 20–33% of patients do not respond to the proposed therapy with available antipsychotic drugs, which is associated with the occurrence of problems with everyday functioning [1].

Currently used drugs are mainly characterized by regulation of the dopaminergic system. Typical neuroleptics inhibit dopamine neurotransmission and act antagonistically on noradrenergic, cholinergic, or histaminergic receptors [2]. In contrast,

atypical antipsychotic drugs affect not only dopamine receptors, but also serotonin receptors [3].

On September 27, 2024, the FDA approved a new oral drug from the biotechnology company Karuna Therapeutics – KarXT (a combination of xanomeline and trospium) for adults with schizophrenia. Three placebo-controlled studies were presented, including one phase II study and two phase III studies. Due to its mechanism of action, this drug indicates a new path for treating positive, negative, and cognitive symptoms of schizophrenia [4, 5]. Currently, research is also underway on the use of this drug in other psychiatric and neurological disorders, including patients with psychosis accompanying Alzheimer's disease [6, 7].

Pharmacokinetics and pharmacodynamics

The innovative drug KarXT (xanomeline-trospium chloride) affects multiple molecular pathways that are involved in schizophrenia, combines a unique dual agonist effect on muscarinic receptors (preferring M1 and M4) and has anticholinergic effects [8, 9]. Higher doses of xanomeline may also affect other subtypes of muscarinic receptors, i.e., M2, M3, and M5 [10, 11]. The effect on the M4 receptor activity results in an enhanced antipsychotic effect, thereby reducing adverse symptoms [12, 13]. Xanomeline also shows affinity for serotonin 5HT1 and 5HT2 receptors [14]. The role of trospium is to non-selectively block peripheral cholinergic effects of the muscarinic agonist. Trospium chloride is characterized by a strong affinity for muscarinic M1, M2, and M3 receptors [15] and practically does not penetrate the blood-brain barrier, therefore adverse effects from the central nervous system are practically unnoticeable [16, 17].

The complex use of two active substances is supposed to prevent the peripheral activity of muscarinic xanomeline [17, 18]. KarXT, in comparison with other drugs used in schizophrenia, does not block dopamine D_2 receptors [5]. Therefore, it is the first drug with such a mechanism of action in the treatment of schizophrenia.

The occurrence of less common and mild adverse effects may be related to the difference in the half-lives of xanomeline ($t_{1/2}$: 1.25 hours) and trospium ($t_{1/2}$: 20 hours) [19, 20]. The time from drug administration to reaching the maximum concentration in the blood (t_{max}) for xanomeline is 2.5 hours. Its bioavailability is very low (<1%) because it is subject to increased first-pass metabolism. It is completely eliminated by the kidneys within 24 hours [10].

For trospium chloride t_{max} is about 4–5 hours [21]. This drug is also characterized by low bioavailability (5–10%), is absorbed slowly, has a low degree of binding to plasma proteins and does not penetrate the blood-brain barrier [22, 23].

Preclinical studies of xanomeline

The pharmacological profile of xanomeline was assessed by Shannon et al. [24]. They compared it to the action of antipsychotic drugs for possible future utility in

the treatment of schizophrenia. Xanomeline produced a dose-dependent reduction in apomorphine-induced climbing in mice (similar to haloperidol, olanzapine, and clozapine) and inhibited non-failure avoidance responses in rats (similar to clozapine and olanzapine). Additionally, it dose-dependently reduced turns, the direction of which was changed by the use of a dopamine agonist in rodents with brain damage by 6-hydroxydopamine, to about 50% of the control value (at a dose of 30 mg/kg). In comparison, olanzapine and clozapine reduced turns to about 5–15% of the control value. Moreover, xanomeline did not induce catalepsy up to 6 hours after drug administration, as is the case with haloperidol [24]. In other studies, this substance, at a dose of 30 mg/kg, proved effective in the conditioned avoidance response (CAR) test in mice and, depending on the dose (3–30 mg/kg), reversed the apomorphine-induced deficit in the prepulse inhibition (PPI) test in rats, which is used as a model of schizophrenia [25, 26].

In summary, the tested substance in preclinical studies, similarly to haloperidol, clozapine, and olanzapine, showed antipsychotic activity [24].

Clinical trials

To date, 5 Phase III clinical trials (NCT04738123, NCT04659161, NCT04659174, NCT04820309, NCT05643170) [27–31] have been completed for KarXT in the treatment of schizophrenia diagnosed according to DSM 5 (*Diagnostic and Statistical Manual of Mental Disorders*). The 5-week NCT04659161 [28] and NCT04738123 [27] studies evaluated the efficacy and safety of xanomeline/trospium monotherapy in patients hospitalized for exacerbation of psychosis. Studies NCT04659174 [29], NCT04820309 [30], and NCT05643170 [31] were additionally designed to analyze the long-term safety, tolerability, and pharmacokinetic characteristics of KarXT. The completion of NCT05643170 [31] was based on a business decision [18].

Recruitment has been announced for 3 studies (NCT05919823 [32], NCT05304767 [33], NCT05145413 [34]) and a new study has been reported, with an estimated start date of 31.12.2024 (NCT06572449) [35]. Studies highlight the long-term effects of using the drug in question (NCT05919823 [32], NCT05304767 [33]) and the effectiveness of therapy as an adjunctive treatment (NCT05145413 [34], NCT05304767 [33]).

In the placebo-controlled studies (NCT04738123, NCT04659161, NCT04659174, NCT04820309, NCT05643170), patients were not allowed to take oral antipsychotics, monoamine oxidase inhibitors, mood stabilizers, anticonvulsants, tricyclic antidepressants, selective serotonin reuptake inhibitors, or any other psychoactive drugs. In addition, participants were allowed to take benzodiazepines (up to 4 mg/day of lorazepam or equivalent, zolpidem, zaleplon, etc.) for the relief of anxiety, agitation, and insomnia. Other medications were not allowed without the consent of the principal investigator unless their use was considered essential. In the KarXT adjunctive therapy evaluation (NCT05145413, NCT05304767), patients received monotherapy with risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine.

Phase I study

A phase I study (NCT02831231 [36]) opened the door to further clinical trials. It was designed to test whether trospium chloride with limited peripheral action would be able to alleviate the adverse effects of xanomeline [37].

The study compared the effect of xanomeline with placebo in monotherapy ($n = 33$) with the effect of xanomeline/trospium formulation ($n = 35$) in recruited, healthy volunteers aged 18–60 years [15]. The study participants gave informed consent to participate in the study and to take contraceptives (women of reproductive age). The recruitment period lasted 21 days. The entire study lasted 9 weeks and was conducted in a single center (double-blind, placebo-controlled study). Participants were given xanomeline at a dose of 75 mg three times a day and trospium at a dose of 20 mg twice a day. For the first 2 days, participants received placebo or trospium. After this time, xanomeline was also included and administered for 7 days. During the study, vital signs such as heart rate, laboratory parameters, and a self-completed visual analogue scale based on the intensity of cholinergic side effects (VAS) were assessed, etc. [37].

Xanomeline has been shown to cause a number of cholinergic side effects. KarXT, on the other hand, reduces these symptoms, i.e., reduces the frequency of 5 side effects by 46% (sweating 48.5% with xanomeline alone vs. 20.0% with KarXT, excessive salivation 36.4% vs. 25.7%, nausea 24.2% vs. 17.1%, diarrhea 21.2% vs. 5.7%, vomiting 15.2% vs. 5.7%). KarXT therefore has a better safety profile. Participants experienced less dizziness and fainting with this medication. There were no differences in vital signs (in terms of electrocardiography results, laboratory parameters, kidney or liver function) [37].

The limitations of this study were: lack of sensitivity of the VAS measures used (results were limited to the lower end of the scale), lack of objective measures of peripheral cholinergic activity and assessment of cholinergic AEs before dosing rather than 2–3 hours after dosing (corresponding to the time needed to reach maximum concentration), lack of a placebo-only group, and inconsistent results regarding the occurrence of diarrhea.

Phase II study

The phase II study (NCT03697252) [38] called EMERGENT-1 was designed to test the safety and efficacy of KarXT. Of the 250 hospitalized patients with schizophrenia, 182 people aged 18–60 were finally qualified for the study. The study was initiated in 12 centers. The screening period itself lasted 7 days. Patients were randomly assigned to two groups: the KarXT group ($n = 90$) and the placebo group ($n = 92$). The drug was administered twice a day for 5 weeks. The study group took xanomeline/trospium in doses from 50 mg to 125 mg of xanomeline and from 20 mg to 30 mg of trospium [15, 17, 39].

89 patients taking KarXT and 90 in the placebo group were included in the safety analysis (total 179 patients). The new drug met the primary endpoint (the most im-

portant for assessing the effect of treatment), i.e., changed the total score on the scale of the *Positive and Negative Syndrome Scale* (PANSS) (in the KarXT group: – 17.4 points and in the placebo group: – 5.9 points). KarXT achieved multiple secondary endpoints: change in the PANSS subitems related to negative symptoms (KarXT group: 3.2 points, placebo group: – 0.9 points). Additionally, it changed the PANSS subitems related to Marder negative symptoms (KarXT: – 3.9 points and placebo group: – 1.3 points). The *Clinical Global Impression-Severity* (CGI-S) scale, which measures the severity of symptoms, also performed favorably (for KarXT: 5.6 points and placebo group: 1.4 points, placebo: $p < 0.001$) [15, 17].

Based on the results, it can be seen that the effect of combined treatment with xanomeline/trospium is characterized by effectiveness in relieving symptoms associated with schizophrenia. This complex drug is well tolerated and has a favorable safety profile, as evidenced by the occurrence of adverse events. In patients, mild and short-term side effects occurred mainly within 1–2 weeks of therapy [15].

Phase I and II studies have shown that adding trospium chloride, a peripherally restricted muscarinic receptor antagonist, to xanomeline reduced the occurrence of adverse events primarily related to gastrointestinal disorders. Moreover, the phase II study confirmed the efficacy, tolerability, and safety of the combination of xanomeline with trospium [40].

Phase III studies

The randomized, double-blind EMERGENT-2 trial (NCT04659161 [28]) included 407 hospitalized patients with schizophrenia and psychotic symptoms from 22 centers in the United States. The results obtained on the PANSS scale were at least 80 points, while in the scale of assessment of positive, negative, depressive, and cognitive symptoms CGI-SCH (*Clinical Global Impression – Schizophrenia*) were equal to or exceeded the value of 4 points.

Two hundred and fifty-two people, aged 18–65 years, who met the criteria were included in the study and randomly assigned to two groups: the study group ($n = 126$) and the placebo group ($n = 126$). The study group took xanomeline/trospium for the first 2 days in doses of 50 mg of xanomeline and 20 mg of trospium, from day 3 to 7 in doses of 100 mg of xanomeline and 20 mg of trospium, from day 8 in doses of up to 125 mg of xanomeline and 30 mg of trospium. Dosing was performed twice a day and lasted until the end of week 5. At any time, it was possible to change the dose to 100 mg of xanomeline and 20 mg of trospium. In week 2, there was a sustained reduction in the severity of psychotic symptoms in the study group until the end of the study. A visible change in the PANSS assessment scale was obtained in week 5 of KarXT. Baseline results were 98.3 points in the KarXT group and 97.9 points in the placebo group [40]. The drug was found to be well tolerated. No movement disorders, weight gain or sedation were observed among patients.

The results of the study confirmed the efficacy and safety profile of KarXT, which was the aim of EMERGENT-2. The most common side effects of the drug were gastrointestinal disorders, i.e., constipation (21%), dyspepsia (19%), nausea (19%), vomiting (14%), diarrhea (6%), reflux (6%). In some patients, headache (14%), hypertension (10%), and dizziness (9%) were also noted [40].

The study NCT04738123 [27] (EMERGENT-3) was another multicenter, randomized, double-blind, placebo-controlled trial in hospitalized patients with acute psychosis and a diagnosis of schizophrenia. The aim was to test the effectiveness and safety of KarXT in people aged 18–65. The study included 256 patients in hospital settings who were assigned to two parallel groups: the KarXT group and the placebo group. For the first 2 days, participants received 50 mg of xanomeline and 20 mg of trospium twice daily, then 100 mg of xanomeline and 20 mg of trospium until day 7, finally reaching 125 mg of xanomeline and 30 mg of trospium between day 8 and 35. There was the possibility of returning to the dosage of 100 mg of xanomeline and 20 mg of trospium in case of adverse events. Tolerability and clinical response were taken into account. The study lasted 5 weeks. The expectation was for a reduction in the total scores of the PANSS positive and negative symptom scales in those taking KarXT and an improvement in the severity of illness symptoms. It was crucial to obtain information on the safety and tolerability of the study drug.

In the Phase 3 EMERGENT-2 [28] and EMERGENT-3 [27] studies, KarXT (FDA-approved as Cobenfy) met its primary endpoint by demonstrating a statistically significant reduction in symptoms of schizophrenia compared with placebo, as measured by the change in the *Positive and Negative Syndrome Scale* (PANSS) total score from baseline to week 5. The drug demonstrated a 9.6-point reduction (-21.2 KarXT vs. – 11.6 placebo; $p < 0.0001$) and an 8.4-point reduction (-20.6 KarXT vs. – 12.2 placebo; $p < 0.0001$) in the PANSS total score compared with placebo at week 5 in EMERGENT-2 [28] and EMERGENT-3 [27], respectively. In the EMERGENT-2 study, KarXT demonstrated statistically significant improvement in illness course from baseline to week 5, as measured by the CGI-S scale, which was a secondary endpoint of the study.

The study NCT04659174 [29] (EMERGENT-4) was designed to evaluate the long-term safety, tolerability, efficacy, and pharmacokinetic characteristics of KarXT in outpatients with schizophrenia. The study group consisted of 156 patients aged 18–65 years who had previously participated in previous clinical trials NCT04659161 [28] and NCT04738123 [27]. This study was a 53-week extension of a short 5-week clinical trial. Therefore, it was of an observational nature. It was conducted at 44 sites. All participants received 50 mg of xanomeline and 20 mg of trospium for the first 2 days, then 100 mg of xanomeline and 20 mg of trospium from day 3 to 7. After day 8, 125 mg of xanomeline and 30 mg of trospium were administered (up to day 364). The drugs were taken twice daily. In case of side effects, it was possible to return to the previous dosage. The study was completed in October 2023.

The aim of the NCT04820309 study [30] (EMERGENT-5) was to evaluate the tolerability and efficacy, characterize the pharmacokinetics of KarXT, and monitor the long-term effects of treatment with this drug. The study was conducted in 64 centers. The study group consisted of outpatients (18-–5 years old) who had not previously participated in clinical trials related to KarXT. The study included 568 people with schizophrenia. All received the drug in the same schedule as before (twice daily). For the first 2 days, patients were given 50 mg of xanomeline and 20 mg of trospium, then from day 3 to 7 100 mg of xanomeline and 20 mg of trospium. The next dose increase occurred on day 8. From day 8 to 364, patients usually took 125 mg of xanomeline and 30 mg of trospium. The dose was reduced to previous values in case of side effects/intolerance. Return to the higher dose was allowed. The reporting date is set for June 30, 2025.

The NCT05643170 [31] is a Phase 3b, 3-year, open-label, multi-center study in which patients with DSM-5 diagnosis of schizophrenia whose current medication(s) is not well tolerated and/or clinical symptoms are not well controlled were switched to receive KarXT. The primary objectives of this study was to assess the long-term safety, tolerability, and efficacy of KarXT, as well as its effect in these patients. Only 4 patients were enrolled in the study. They were given 50 mg of xanomeline and 20 mg of trospium twice daily, then 100 mg of xanomeline and 20 mg of trospium, and finally 125 mg of xanomeline and 30 mg of trospium according to the schemes of previous studies. The *Investigator Assessment Questionnaire* (IAQ), *Clinical Global Impression* (CGI), *Clinical Global Impression – Severity of Illness* (CGI-S), *Clinical Global Impression – Improvement* (CGI-I), etc. were used for the assessment. The study was completed in March 2023 but no results were posted.

Clinical trials during recruitment

The NCT05919823 study [32] (UNITE-001) aims to evaluate the efficacy and safety (including long-term) of KarXT in hospitalized patients diagnosed with schizophrenia with an acute course of psychosis. The study is conducted in 29 centers. The study group consists of people aged 18–65 years from the Chinese population. It is estimated that 158 people will participate in the study. The trial consists of two parts. The first part, i.e., double-blind – concerns randomized, parallel groups with placebo control. The drug dosing takes into account 5 weeks and its schedule is identical to that in the studies already completed. The second part is a 12-week extended open evaluation. The study is planned to end in May 2025.

The 6-week NCT05145413 [34] (ARISE) study is evaluating the efficacy and safety of KarXT add-on therapy in outpatients with an inadequate response to current antipsychotic therapy. The research centers are located in 159 sites. Participants are randomly assigned to two double-blind groups: the study group and the placebo group. The estimated number of participants is 400. The dosage is as follows: initially 50 mg of xanomeline and 20 mg of trospium, then 75 mg of xanomeline and 20 mg of

trospium, then 100 mg xanomeline and 20 mg of trospium, up to 125 mg of xanomeline and 30 mg of trospium (in each case twice daily). The study is scheduled to end in February 2025.

The aim of the 52-week study NCT05304767 [33] is to extend the long-term safety and tolerability of KarXT as adjunctive therapy in outpatients with inadequately controlled symptoms of schizophrenia. The study group from 152 centers consists of patients who previously completed treatment in the NCT05145413 (ARISE) study. The number of participants in this trial is estimated to be 280, aged 18–59 years. The xanomeline/trospium dosing regimen is appropriate for the NCT05145413 (ARISE) study. Patients continue to receive antipsychotics in addition to KarXT. The study is expected to be completed in February 2026.

New registered clinical trial

The planned start date of the NCT06572449 study [35] is December 2024. The study objectives are to assess the safety and efficacy of a gradually increasing dose of KarXT and to assess the effect of food on KarXT treatment in patients with schizophrenia. It is expected to recruit 100 participants from 5 centers. The planned end date of the study is August 2025.

Side effects

The side effects of KarXT include nausea, vomiting, constipation, headache, dizziness, hypertension, dry mouth, which may be the reason for discontinuation of treatment. These gastrointestinal disorders may be related to the activation of M1 receptors [41]. These symptoms are mainly cholinergic in nature and are not in any way related to the typical symptoms resulting from disorders of the pyramidal tract function, that occur when using other drugs for schizophrenia, i.e., there is no motor agitation, a sense of needing to be in motion, movement disorders/sudden movements, limb tremors, slowness of movement, problems with walking or muscle stiffness [4]. Another big advantage is that there are no metabolic effects, such as weight gain, lipid disorders, or glucose concentration [40].

KarXT for Alzheimer's disease-related psychosis

Currently, 3 clinical trials are being conducted (NCT05511363 [42], NCT06126224 [43], NCT05980949 [44]) investigating KarXT for the treatment of Alzheimer's disease-related psychosis. The 38-week randomized, double-blind, placebo-controlled, multicenter outpatient study NCT05511363 [42] (ADEPT-1) is testing whether KarXT prevents relapse in people with Alzheimer's disease-related psychosis. It is assessing the time from randomization to discontinuation for any reason, as well as safety and tolerability in these patients. Qualification is to include 380 patients aged 55–90 years.

The following KarXT doses were determined: 20/2 mg; 30 mg/3 mg; 40 mg/4 mg; 50 mg/5 mg and 66.7/6.67 (3 times a day).

The next study, NCT06126224 [43] (ADEPT-2), is evaluating the efficacy and safety of KarXT in individuals aged 55 to 90 years with mild to severe Alzheimer's disease (AD) with moderate to severe AD-related psychosis. This is a phase 3, randomized, double-blind, placebo-controlled, parallel-group study. 400 participants are expected to participate. The daily dosage of KarXT is to range from 60/6 mg to 200/20 mg.

A 54-week open-label extension, multicenter, phase 3 roll-over study NCT05980949 [44] (ADEPT-3) is intended to assess the long-term safety and tolerability of KarXT in patients with psychosis associated with Alzheimer's disease (AD). Subjects (randomized or non-randomized) who complete 38 weeks of ADEPT-1 or ADEPT-2 will be eligible to enter ADEPT-3. The estimated number of participants is 140 [42–44].

Limitations of clinical trials

The KarXT studies were short-term (five weeks) and therefore did not allow for the examination of relapse, which may be a better indicator of the drug's long-term effectiveness. Furthermore, the KarXT studies and some studies of other antipsychotic drugs included for comparison were conducted in hospitalized patients (during the study) diagnosed with schizophrenia. Hospitalized individuals tend to exhibit more severe symptoms of schizophrenia than non-hospitalized individuals, and thus the studies may represent a subgroup of patients with more severe symptoms.

Short-term studies have shown that KarXT is a comparable antipsychotic drug in terms of clinical efficacy when compared to other antipsychotic drugs [45]. KarXT was significantly less likely to cause weight gain, a problematic side effect of antipsychotics, than risperidone or olanzapine. However, only long-term data will provide information on the relative efficacy and safety of KarXT. If long-term studies of KarXT support the data from short-term studies, this will be crucial information for clinicians and patients. In particular, long-term data will be essential to investigate the risk of developing conditions associated with antipsychotics that have lasting health consequences, such as tardive dyskinesia, metabolic syndrome, or hyperprolactinemia, which cannot be reliably measured in short-term studies. Early evidence from long-term studies seems promising [29, 30, 40].

Recapitulation

KarXT (FDA-approved as Cobenfy) is the first of several next-generation drug candidates designed to engage muscarinic receptors in the brain. Cobenfy is currently not available in Europe and it is not known when it will be available in Poland. KarXT, with its novel mechanism of action, has the potential to become the first muscarinic

receptor-activating drug for schizophrenia [40]. The primary goal of KarXT is to improve cognitive function and improve psychotic symptoms in patients while minimizing the occurrence of significant adverse events. The FDA approval of Cobenfy is supported by data from the EMERGENT clinical program, which includes three placebo-controlled efficacy and safety studies and two open-label studies evaluating the long-term safety and tolerability of Cobenfy for up to one year. In the Phase 3 EMERGENT-2 and EMERGENT-3 studies, Cobenfy met its primary endpoint, demonstrating a statistically significant reduction in schizophrenia symptoms compared with placebo, as measured by the change from baseline to week 5 on the *Positive and Negative Syndrome Scale* (PANSS) total score. Clinical studies regarding KarXT are presented in Table below.

The development of KarXT represents a promising approach to improving treatment options for people with schizophrenia and Alzheimer's disease. This advance makes schizophrenia treatment more tailored to individual needs – providing an alternative for many who do not benefit from current treatments or abandon them because of intolerable side effects. Data on the long-term efficacy and safety of KarXT are needed to increase the certainty of conclusions and provide crucial information on neurological side effects, in particular tardive dyskinesia.

Table. **The research on Cobenfy (known as KarXT)**

Identifier clinicaltrials.gov	Title of study	References
PHASE I		
NCT02831231	*Pilot Study Comparing Effects of Xanomeline Alone to Xanomeline Plus Trospium. Official Title: A Phase I, Double-Blind, Randomized, Multiple-Dose, Pilot Study Comparing Xanomeline Administered Alone to Xanomeline Administered in Combination With Trospium Chloride in Normal Healthy Volunteers*	[36]
PHASE II		
NCT03697252 (EMERGENT-1)	*A Study to Assess Safety and Efficacy of KarXT in Adult Patients With Schizophrenia (EMERGENT-1). Official Title: A Phase 2, Randomized, Double-blinded Study to Assess the Safety, Tolerability, and Efficacy of KarXT in Hospitalized Adults With DSM-5 Schizophrenia*	[38]
PHASE *III*		
NCT04659161 (EMERGENT-2)	*A Study to Assess Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adult Patients With Schizophrenia (EMERGENT-2). Official Title: A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults With DSM-5 Schizophrenia*	[28]

table continued on the next page

NCT04738123 (EMERGENT-3)	*A Study to Assess Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adult Patients With Schizophrenia (EMERGENT-3). Official title: A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults With DSM-5 Schizophrenia*	[27]
NCT04659174 (EMERGENT-4)	*An Extension Study to Assess Long-term Safety, Tolerability, and Efficacy of KarXT in Adult Patients With Schizophrenia (EMERGENT-4). Official Tittle: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects With DSM-5 Schizophrenia*	[29]
NCT04820309 (EMERGENT-5)	*An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Adult Patients With Schizophrenia (EMERGENT-5). Official Title: An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in De Novo Subjects With DSM-5 Schizophrenia*	[30]
NCT05643170 (PENNANT)	*An Open-label Study to Assess the Long-term Safety, Tolerability, Effectiveness, and Durability of Effect of KarXT in Patients With DSM-5 Diagnosis of Schizophrenia (PENNANT). Official Title: A Multi-center, Open-label Study to Assess the Effectiveness, Long-term Safety, Tolerability, and Durability of Effect of KarXT in Patients With DSM-5 Diagnosis of Schizophrenia*	[31]
RESEARCH IN PROGRESS		
NCT05511363 (ADEPT-1)	*A Study to Assess Efficacy and Safety of KarXT for the Treatment of Psychosis Associated With Alzheimer's Disease (ADEPT-1). Official Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Relapse Prevention Study to Evaluate the Safety and Efficacy of KarXT for the Treatment of Psychosis Associated With Alzheimer's Disease*	[42]
NCT05919823 (UNITE-001)	*A Study to Assess the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Chinese Adult Subjects With DSM-5 Schizophrenia (UNITE-001). Official Title: A Phase 3, Multicenter, Two-part Study With a 5-week Double-blind Part (Randomized, Parallel-group, Placebo-controlled) Followed by a 12-week Open-label Extension Part, to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Chinese Adult Subjects With DSM-5 Schizophrenia*	[32]

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NCT06126224 (ADEPT-2)	*A Study to Assess Efficacy and Safety of KarXT for the Treatment of Psychosis Associated With Alzheimer's Disease (ADEPT-2). Official Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of KarXT for the Treatment of Psychosis Associated With Alzheimer's Disease*	[43]
NCT05304767	*An Extension Study to Assess Long-Term Safety and Tolerability of Adjunctive KarXT in Subjects With Inadequately Controlled Symptoms of Schizophrenia. Official Title: An Open-label Extension Study to Assess the Long-term Safety and Tolerability of Adjunctive KarXT in Subjects With Inadequately Controlled Symptoms of Schizophrenia*	[33]
NCT05980949 (ADEPT-3)	*Open-Label Extension Study to Assess the Long-Term Safety and Tolerability of KarXT in Subjects With Psychosis Associated With Alzheimer's Disease (ADEPT-3). Official Title: A Phase 3 Global, Multicenter, Open-Label Extension Study to Assess the Long-Term Safety and Tolerability of KarXT in Subjects With Psychosis Associated With Alzheimer's Disease*	[44]

References

1. Ackenheil M, Weber K. *Differing response to antipsychotic therapy in schizophrenia: Pharmacogenomic aspects*. Dialogues Clin. Neurosci. 2004; 6(1): 71–77. Doi: 10.31887/DCNS.2004.6.1/mackenheil.
2. Drummond N, McCleary L, Freiheit E, Molnar F, Dalziel W, Cohen C et al. *Antidepressant and antipsychotic prescribing in primary care for people with dementia*. Can. Fam. Physician. 2018; 64(11): e488–e497.
3. Olagunju AT, Clark SR, Baune BT. *Long-acting atypical antipsychotics in schizophrenia: A systematic review and meta-analyses of effects on functional outcome*. Aust. N. Z. J. Psychiatry 2019; 53(6): 509–527. Doi: 10.1177/0004867419837358.
4. DeBattista C, Schatzberg AF. *The Black Book of Psychotropic Dosing and Monitoring*. Psychopharmacol. Bull. 2024; 54(3): 8–59.
5. Correll CU, Tusconi M, Carta MG, Dursun SM. *What remains to be discovered in schizophrenia therapeutics: Contributions by advancing the molecular mechanisms of drugs for psychosis and schizophrenia*. Biomolecules 2024; 14(8): 906. Doi: 10.3390/biom14080906.
6. 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(8): 717–726. Doi: 10.1056/NEJMoa2017015.
7. Singh B. *Schizophrenia as a problem of other minds*. Philos. Psychiatry Psychol. 2021; 28(3): 1–18. Doi: 10.1353/ppp.2021.0040.
8. Kondej M, Stępnicki P, Kaczor AA. *Multi-target approach for drug discovery against schizophrenia*. Int. J. Mol. Sci. 2018; 19(10): 3105. Doi: 10.3390/ijms19103105.
9. Dencker D, Wörtwein G, Weikop P, Jeon J, Thomsen M, Sager TN et al. *Involvement of a subpopulation of neuronal M4 muscarinic acetylcholine receptors in the antipsychotic-like effects of the M1/M4 preferring muscarinic receptor agonist xanomeline*. J. Neurosci. 2011; 31(6): 5905–5908. Doi: 10.1523/JNEUROSCI.0370-11.2011.
10. Mirza NR, Peters D, Sparks RG. *Xanomeline and the antipsychotic potential of muscarinic receptor subtype selective agonists*. CNS Drug Rev. 2003; 9(2): 159–186.
11. Thorn CA, Moon J, Bourbonais CA, Harms J, Edgerton JR, Stark E et al. *Striatal, hippocampal, and cortical networks are differentially responsive to the M4 – and M1-muscarinic acetylcholine receptor mediated effects of xanomeline*. ACS Chem. Neurosci. 2019; 10(2): 1753–1764. Doi: 10.1111/j.1527-3458.2003.tb00247.x.
12. Tzavara ET, Bymaster FP, Davis RJ, Wade MR, Perry KW, Wess J et al. *M4 muscarinic receptors regulate the dynamics of cholinergic and dopaminergic neurotransmission: Relevance to the pathophysiology and treatment of related CNS pathologies*. FASEB J. 2004; 18(12): 1410–1412. Doi: 10.1096/fj.04-1575fje.
13. Bubser M, Bridges TM, Dencker D, Gould RW, Grannan M, Noetzel MJ et al. *Selective activation of M4 muscarinic acetylcholine receptors reverses MK-801-induced behavioral impairments and enhances associative learning in rodents*. ACS Chem. Neurosci. 2014; 5(10): 920–942. Doi: 10.1021/cn500128b.
14. Watson J, Brough S, Coldwell MC, Gager T, Ho M, Hunter AJ et al. *Functional effects of the muscarinic receptor agonist, xanomeline, at 5-HT1 and 5-HT2 receptors*. Br. J. Pharmacol. 1998; 125(7): 1413–1420. Doi: 10.1038/sj.bjp.0702201.
15. Azargoonjahromi A. *Current findings and potential mechanisms of KarXT (xanomeline-trospium) in schizophrenia treatment*. Clin. Drug Investig. 2024; 44(7): 471–493. Doi: 10.1007/s40261-024-01377-9.

16. Staskin D, Kay G, Tannenbaum C, Goldman HB, Bhashi K, Ling J et al. *Trospium chloride is undetectable in the older human central nervous system*. J. Am. Geriatr. Soc. 2010; 58(8): 1618–1619. Doi: 10.1111/j.1532-5415.2010.02988.x.

17. 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 (Heidelb.). 2022; 8(1): 109. Doi: 10.1038/s41537-022-00320-1.

18. Dudzik P, Lustyk K, Pytka K. *Beyond dopamine: Novel strategies for schizophrenia treatment*. Med. Res. Rev. 2024; 44(5): 2307–2330.

19. Bender AM, Jones CK, Lindsley CW. *Classics in chemical neuroscience: Xanomeline*. ACS Chem. Neurosci. 2017; 8(3): 435–443. Doi: 10.1021/acschemneuro.7b00001.

20. Jakubík J, Tucek S, El-Fakahany EE. *Allosteric modulation by persistent binding of xanomeline of the interaction of competitive ligands with the M1 muscarinic acetylcholine receptor*. J. Pharmacol. Exp. Ther. 2002; 301(3): 1033–1041. Doi: 10.1124/jpet.301.3.1033.

21. Zhang R, Yuan G, Li R, Liu X, Wei C, Wang B et al. *Pharmacokinetic and bioequivalence studies of trospium chloride after a single-dose administration in healthy Chinese volunteers*. Arzneimittelforschung 2012; 62(5): 247–251. Doi: 10.1055/s-0032-1304649.

22. Albrecht H, Bruhn R, Lorenz D, Lücker PW, Schumacher M. *Pupillometry: A non-invasive pharmacokinetic and pharmacodynamic method to study the action of trospium chloride (Spasmo-lyt) on smooth muscle*. Methods Find. Exp. Clin. Pharmacol. 1983; 5(8): 585–587.

23. Doroshyenko O, Jetter A, Odenthal KP, Fuhr U. *Clinical pharmacokinetics of trospium chloride*. Clin. Pharmacokinet. 2005; 44(7): 701–720. Doi: 10.2165/00003088-200544070-00003.

24. Shannon HE, Rasmussen K, Bymaster FP, Hart JC, Peters SC, Swedberg MD et al. *Xanomeline, an M(1)/M(4) preferring muscarinic cholinergic receptor agonist, produces antipsychotic-like activity in rats and mice*. Schizophr. Res. 2000; 42(3): 249–259. Doi: 10.1016/s0920-9964(99)00138-3.

25. Shannon HE, Hart JC, Bymaster FP, Calligaro DO, DeLapp NW, Mitch CH et al. *Muscarinic receptor agonists, like dopamine receptor antagonist antipsychotics, inhibit conditioned avoidance response in rats*. J. Pharmacol. Exp. Ther. 1999; 290(2): 901–907.

26. Stanhope KJ, Mirza NR, Bickerdike MJ, Bright JL, Harrington NR, Hesselink MB et al. *The muscarinic receptor agonist xanomeline has an antipsychotic-like profile in the rat*. J. Pharmacol. Exp. Ther. 2001; 299(2): 782–792.

27. Karuna Therapeutics. *A Study to Assess Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adult Patients With Schizophrenia (EMERGENT-3)*. Official Title: *A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults With DSM-5 Schizophrenia*. https:// https://clinicaltrials.gov/study/NCT04738123.

28. Karuna Therapeutics. *A Study to Assess Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adult Patients With Schizophrenia (EMERGENT-2)*. Official Title: *A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults With DSM-5 Schizophrenia*. https://clinicaltrials.gov/study/NCT04659161.

29. Karuna Therapeutics. *An Extension Study to Assess Long-term Safety, Tolerability, and Efficacy of KarXT in Adult Patients With Schizophrenia (EMERGENT-4)*. Official Title: *An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects With DSM-5 Schizophrenia*. https://clinicaltrials.gov/study/NCT04659174.

30. Karuna Therapeutics. *An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Adult Patients With Schizophrenia (EMERGENT-5)*. Official Title: *An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in De Novo Subjects With DSM-5 Schizophrenia*. https://clinicaltrials.gov/study/NCT04820309.
31. Karuna Therapeutics. *An Open-Label Study to Assess the Long-Term Safety, Tolerability, Effectiveness, and Durability of Effect of KarXT in Patients with DSM-5 Diagnosis of Schizophrenia (PENNANT)*. https://clinicaltrials.gov/study/NCT05643170 (retrieved: 9.03.2024).
32. Karuna Therapeutics. *A Study to Assess the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Chinese Adult Subjects With DSM-5 Schizophrenia (UNITE-001)*. https://clinicaltrials.gov/study/NCT05919823.
33. Karuna Therapeutics. *An Extension Study to Assess Long-Term Safety and Tolerability of Adjunctive KarXT in Subjects With Inadequately Controlled Symptoms of Schizophrenia*. https://clinicaltrials.gov/study/NCT05304767 (study completion (estimated) 27 February 2026).
34. Karuna Therapeutics. *A Study to Assess Efficacy and Safety of Adjunctive KarXT in Subjects With Inadequately Controlled Symptoms of Schizophrenia (ARISE)*. https://clinicaltrials.gov/study/NCT05145413 (study completion (estimated) 28 February 2025).
35. Karuna Therapeutics. *A Phase 3b, Open-label, Multicenter, Two-Period, Slow-titration and Food Effect Study to Assess the Safety and Efficacy of KarXT in Participants With DSM-5 Schizophrenia*. https://clinicaltrials.gov/study/NCT06572449 (study completion (estimated) 08 August 2025).
36. Karuna Therapeutics. *Pilot Study Comparing Effects of Xanomeline Alone to Xanomeline Plus Trospium*. Official Title: *A Phase I, Double-Blind, Randomized, Multiple-Dose, Pilot Study Comparing Xanomeline Administered Alone to Xanomeline Administered in Combination With Trospium Chloride in Normal Healthy Volunteers*. https://clinicaltrials.gov/study/NCT02831231.
37. 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 (Berl.). 2023; 240(5): 1191–1198. Doi: 10.1007/s00213-023-06362-2.
38. Karuna Therapeutics. *A Study to Assess Safety and Efficacy of KarXT in Adult Patients With Schizophrenia (EMERGENT-1)*. Official Title: *A Phase 2, Randomized, Double-blinded Study to Assess the Safety, Tolerability, and Efficacy of KarXT in Hospitalized Adults With DSM-5 Schizophrenia*. https://clinicaltrials.gov/study/NCT03697252.
39. 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(3): 21m14316. Doi: 10.4088/JCP.21m14316.
40. Kaul I, Sawchak S, Correll CU, Kakar R, Breier A, Zhu H et al. *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*. Lancet 2024; 403(10422): 160–170. Doi: 10.1016/S0140-6736(23)02190-6.
41. Singh A. *Xanomeline and trospium: A potential Fixed Drug Combination (FDC) for schizophrenia – A brief review of current data*. Innov. Clin. Neurosci. 2022; 19(10–12): 43–47.
42. Karuna Therapeutics. *A Study to Assess Efficacy and Safety of KarXT for the Treatment of Psychosis Associated With Alzheimer's Disease (ADEPT-1)*. https://clinicaltrials.gov/study/NCT05511363 (study completion (estimated) 05 October 2025).
43. Karuna Therapeutics. *A Study to Assess Efficacy and Safety of KarXT for the Treatment of Psychosis Associated With Alzheimer's Disease (ADEPT-2)*. https://clinicaltrials.gov/study/NCT06126224 (study completion (estimated) 31 July 2025).

44. Karuna Therapeutics. *Open-Label Extension Study to Assess the Long-Term Safety and Tolerability of KarXT in Subjects With Psychosis Associated With Alzheimer's Disease (ADEPT-3)*. https://clinicaltrials.gov/study/NCT05980949 (study completion (estimated) 30 April 2026)
45. Wright AC, McKenna A, Tice JA, Rind DM, Agboola F. *A network meta-analysis of KarXT and commonly used pharmacological interventions for schizophrenia*. Schizophr. Res. 2024; 274: 212–219. Doi: 10.1016/j.schres.2024.09.023.

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