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

Peter J. Weiden, MD[a,*]; Alan Breier, MD[b]; Sarah Kavanagh, MPH[c]; Andrew C. Miller, PhD[a]; Stephen K. Brannan, MD[a]; and Steven M. Paul, MD[a]

ABSTRACT

Objective: To evaluate Positive and Negative Syndrome Scale (PANSS) categorical response rates, time course of response, and symptom subdomains of response with the combination oral agent KarXT (xanomeline–trospium) in the treatment of schizophrenia.

Methods: Post hoc analysis was conducted for EMERGENT-1 (NCT03697252), a 5-week, inpatient, placebo-controlled, phase 2 study of acute psychosis in patients who met *DSM-5* criteria for schizophrenia. The EMERGENT-1 study was conducted between September 2018 and August 2019. Categorical thresholds of response used were PANSS total score reductions of ≥ 20%, ≥ 30%, ≥ 40%, and ≥ 50% between baseline and study end. Number needed to treat (NNT) for each categorical threshold was calculated. The proportion of KarXT- and placebo-treated patients achieving each response threshold at weeks 2, 4, and 5 was assessed. Marder 5-factor analysis of PANSS assessed response with KarXT across symptom domains.

Results: A total of 83 patients in the KarXT group and 87 patients in the placebo group were included in the modified intent-to-treat analysis. Response rates with KarXT ranged from 59.0% for a ≥ 20% threshold to 15.7% for a ≥ 50% threshold. All response rates with KarXT were significantly higher than in the placebo arm ($P < .05$), with NNTs ranging from 3 (≥ 20% improvement) to 11 (≥ 50% improvement). KarXT was associated with a significantly higher response rate relative to placebo as early as 2 weeks for ≥ 20% ($P = .0001$) and ≥ 30% ($P = .0022$) thresholds and at 4 weeks for the ≥ 40% ($P = .0049$) and ≥ 50% ($P = .0041$) thresholds. Each of the Marder 5 factors showed significant differences favoring KarXT over placebo ($P < .05$) by 2 weeks and continuing through week 5 (endpoint Cohen *d* effect sizes, 0.48–0.66).

Conclusions: KarXT provided clinically meaningful responder rates on PANSS total score compared with placebo at each response threshold, providing further support of the successful primary and secondary endpoints. Response was demonstrated as early as 2 weeks relative to placebo. KarXT demonstrated improvements vs placebo in all 5 factors (positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility, and anxiety/depression).

Trial Registration: ClinicalTrials.gov identifier: NCT03697252

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[a]Karuna Therapeutics, Boston, Massachusetts
[b]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana
[c]Kavanagh Statistical Consulting, Apex, North Carolina
**Corresponding author:* Peter J. Weiden, MD, Karuna Therapeutics, 99 High St, Floor 26, Boston, MA 02110 (pweiden@karunatx.com).

All current antipsychotic drugs used to treat schizophrenia have direct dopamine D_2-receptor blocking activity and, thus, share a common mechanism of action.[1] Although they are usually effective in controlling positive symptoms and preventing relapse, there is little evidence that current antipsychotics substantially improve negative or cognitive symptoms.[2] Further, direct D_2 dopamine antagonism is associated with a range of problems, such as antipsychotic-induced parkinsonism, prolactin elevation, and risk of tardive dyskinesia. For these reasons, there have been long-standing efforts to find pharmacologic treatments that offer antipsychotic efficacy without direct antagonism of the dopamine D_2 receptor.

Muscarinic receptors have shown promise as therapeutic targets for antipsychotic drug development dating back to the 1990s, when xanomeline, an M_1/M_4-preferring muscarinic receptor agonist initially developed for cognitive symptoms of Alzheimer's disease, was unexpectedly found to reduce psychotic symptoms associated with dementia.[3] This observation prompted further work evaluating xanomeline's antipsychotic properties. In preclinical studies, xanomeline had no direct affinity for dopamine receptors and its antipsychotic activity was mediated by central muscarinic receptors.[4,5] In a small, randomized, double-blind, proof-of-concept study in acutely psychotic patients with schizophrenia, xanomeline showed symptom improvement as measured by Positive and Negative Syndrome Scale (PANSS) total score in xanomeline-treated patients compared with those receiving placebo.[6] However, further development of xanomeline was hampered because of unwanted side effects commonly associated with muscarinic receptor agonists, sometimes referred to as "procholinergic" side effects (eg, nausea, vomiting, and diarrhea).[7] These tolerability problems are a well-known class effect of muscarinic receptor agonists and

Clinical Points

- KarXT (xanomeline–trospium) is a central muscarinic receptor agonist without direct affinity for dopamine receptors.
- KarXT demonstrated efficacy in schizophrenia in a 5-week, phase 2, inpatient study, providing evidence that muscarinic receptor agonists may be a new approach to treating schizophrenia.
- This article reports additional PANSS outcomes, including categorical response rates, time course of response, and improvement across broader symptom domains.

are believed to be the result of activation of peripheral muscarinic receptors.

The combination oral agent KarXT (xanomeline–trospium) was developed to address the problem of unwanted stimulation of peripheral muscarinic receptors by xanomeline while preserving its muscarinic receptor agonist effects in the central nervous system (CNS). KarXT combines xanomeline with trospium, a US Food and Drug Administration–approved peripheral muscarinic receptor antagonist commonly used for overactive bladder. Trospium does not cross the blood-brain barrier, so it counteracts xanomeline's peripheral muscarinic receptor agonism without impacting xanomeline's activity in the CNS.[8] Relative to xanomeline alone, KarXT has been reported to be associated with fewer and less severe procholinergic side effects.[9]

In a recent phase 2 study, KarXT successfully met its primary efficacy and safety objectives as an investigational treatment for patients with schizophrenia.[10] Briefly, the primary results showed a statistically significant difference in change from baseline to week 5 in PANSS total score (−17.4 points for KarXT vs −5.9 points for placebo; 95% confidence interval [CI], −16.1 to −7.1; $P < .001$). The results for most of the secondary endpoints, including PANSS positive and negative symptom subscales and Clinical Global Impression–Severity (CGI-S) endpoints, also favored the KarXT group. Safety results are detailed in the primary publication but are briefly summarized here. The adverse event (AE) profile of KarXT was consistent with the procholinergic AEs of a muscarinic agonist, such as xanomeline, and the peripheral anticholinergic AEs were consistent with those of trospium (eg, constipation and dry mouth).[11] All procholinergic/anticholinergic AEs were rated as mild or moderate (Common Terminology Criteria for Adverse Events grade 1 or 2), and none resulted in early discontinuation from the clinical trial.[10] These encouraging results form the basis of an ongoing phase 3 program investigating KarXT for the treatment of acute psychosis in schizophrenia.

Until the phase 3 data are available, the phase 2 study remains the primary source of efficacy information for KarXT. The primary publication focuses on the prospective statistical hierarchy of analysis that is required in registration studies. Here, we present additional analysis focused on domains of response and categorical outcomes that may help guide clinical decision-making.[12] Categorical outcomes are anchored to the expectations of treatment efficacy, duration of exposure, and the severity of the symptoms of the disorder being studied. The latter are often calibrated against the anticipated efficacy within the treatment population to assess magnitude of clinical response.[13] For short-term treatment of psychosis in patients with schizophrenia, it is common to choose 1 or more thresholds of symptom response achieved (eg, ranging from ≥ 20% improvement to ≥ 50% improvement in aggregate symptoms) between the start and end of the treatment period.[14]

Here, we provide additional, previously unpublished results of secondary and post hoc efficacy analyses to answer the following questions: (1) What are the categorical response rates associated with KarXT treatment assessed by PANSS total scores from baseline to the end of the study? (2) What is the clinical magnitude of these responses using a number needed to treat (NNT) analysis based on differences between KarXT and placebo at endpoint? (3) What is the time to reach these responses using PANSS assessments at 2 and 4 weeks? (4) What are the symptom domains of response beyond just positive and negative symptoms assessed using a 5-factor PANSS instead of the original 3 PANSS subscales?

METHODS

Study Design

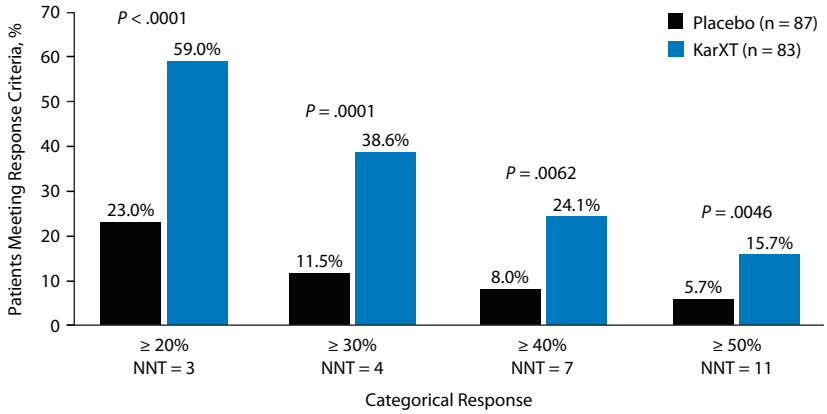
This was a post hoc analysis from a phase 2, randomized, double-blind trial of KarXT vs placebo (EMERGENT-1; ClinicalTrials.gov identifier NCT03697252) for acutely psychotic adults with schizophrenia.[10] The EMERGENT-1 study was conducted between September 2018 and August 2019. Details of the trial methods, population, safety, and the prespecified primary and secondary endpoints have been previously published.[10] Briefly, after a 7-day screening period, participants were randomized 1:1 to receive either oral KarXT or matched placebo twice daily for 5 weeks of inpatient treatment. The dosing schedule of KarXT (mg xanomeline/mg trospium) was flexible, starting with 50 mg/20 mg twice daily and increasing to a maximum of 125 mg/30 mg twice daily.

A central institutional review board approved the study protocol and amendments. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. All patients provided written informed consent prior to participation.

Study Population

At study entry, patients aged 18–60 years with a primary diagnosis of schizophrenia based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), were enrolled.[15] Other key inclusion criteria included recent worsening of positive symptoms warranting hospitalization, a PANSS total score > 80, and a CGI-S score of 4 (moderately ill) or higher. Patients with a primary disorder other than schizophrenia within the 12 months preceding screening, a history of treatment resistance to antipsychotic medications,

Figure 1. PANSS Categorical Responses at Week 5 Using 4 Cutoff Criteria



Abbreviations: NNT = number needed to treat, PANSS = Positive and Negative Syndrome Scale.

or a decrease in the PANSS total score ≥ 20% between screening and baseline were excluded.

Efficacy Measures

The PANSS was the primary assessment used for efficacy outcomes of the study. PANSS is a 30-item symptom severity measure typically used in treatment studies of schizophrenia (Supplementary Table 1).[16] PANSS assessments occurred at baseline, week 2, week 4, and week 5 (or last assessment for early discontinuation). The primary prespecified outcome was the KarXT–placebo difference in change from baseline to week 5 in PANSS total score. Secondary prespecified outcomes included PANSS positive and negative subscales and CGI-S outcomes. The CGI-S is a 7-point scale that requires the investigator to rate the severity of the patient's illness relative to the investigator's prior experience with patients with the same diagnosis.[17]

Categorical Response Definitions

For the present post hoc analysis, a series of prespecified percentage improvements in PANSS total score between baseline and endpoint was used to assess categorical response. For this analysis, a total of 4 thresholds were chosen: ≥ 20%, ≥ 30%, ≥ 40%, and ≥ 50% reduction in PANSS total score at endpoint compared with baseline. These thresholds have been used in the literature reporting on categorical response outcomes from clinical trials of antipsychotic treatment in patients with schizophrenia.[14,18]

Time Course of Response

The time course of response was evaluated based on the PANSS total score obtained at each postbaseline assessment (2 weeks, 4 weeks, and 5 weeks), using the same 4 thresholds (≥ 20%, ≥ 30%, ≥ 40%, and ≥ 50% reduction) but considering earlier timepoints.

Symptom Domains of Response

A Marder 5-factor model of the PANSS[19] was used to assess symptom domains of response. The 5 Marder factors consist of positive symptom, negative symptom, disorganized thought, uncontrolled hostility, and anxiety/depression factors (see Supplementary Table 2 for a list of items included in each factor).

Statistical Analyses

Analyses were performed for the modified intent-to-treat population (mITT), which was the prespecified population for the primary and secondary endpoints. The mITT population was defined as all randomized patients who received at least 1 dose of study medication, had a baseline PANSS assessment, and had at least 1 postbaseline PANSS assessment.

Responder and Time Course Analyses

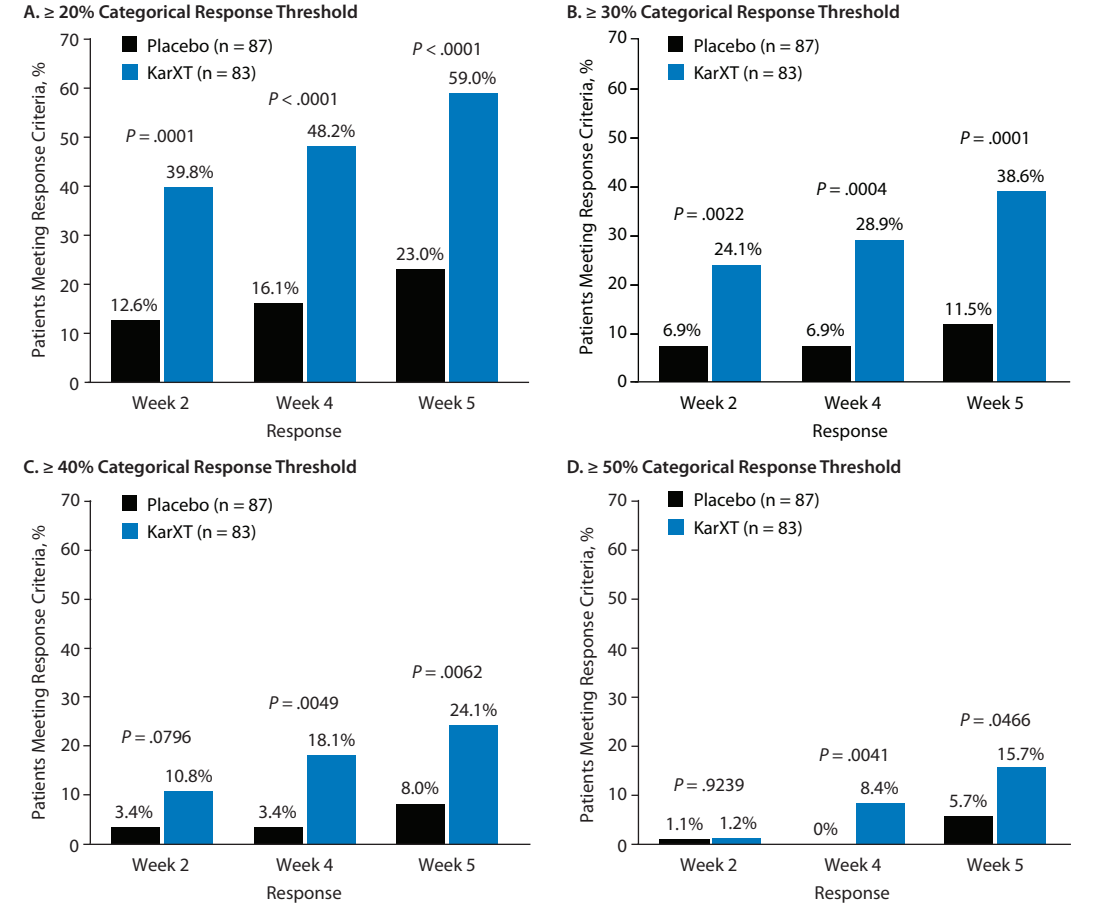
For all PANSS categorical response analyses, PANSS response rates transformed the original 1- to 7-item range to a 0- to 6-item range, according to recent recommendations for PANSS categorical outcomes.[20,21] For this transformation, the original scores were simply reduced by 1 point for the purposes of analysis (ie, original scores of 1 were reset to 0, original scores of 2 were reset to 1, and so forth).

The primary efficacy endpoint in the study was the difference between the placebo arm and active-treatment arm in continuous change from baseline in PANSS total score at week 5, analyzed using a mixed model for repeated measures (MMRM) for group differences in the least-squares mean (LSM) change. For this post hoc analysis, logistic regression models were used to compare PANSS response rates in each treatment group, adjusting for factors of age, sex, and treatment group. Differences between KarXT and placebo were estimated using odds ratios, 95% CIs, and nominal *P* values. The NNT at 5 weeks was calculated as 1 divided by the difference in the PANSS responder rates for KarXT and placebo. Missing data were imputed using last-observation-carried-forward methodology.

Symptom Domains of Response

For response based on a PANSS 5-factor analysis, change from baseline in each of the 5 factors was analyzed using MMRM, with the observed change-from-baseline score at each visit as the response, including treatment group, visit,

Figure 2. PANSS Categorical Response by Study Week: (A) ≥ 20%, (B) ≥ 30%, (C) ≥ 40%, and (D) ≥ 50% Reduction in PANSS Total Score



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

and the interaction of treatment group and visit as fixed effects and baseline score, site, age, and sex as covariates. Differences between KarXT and placebo were estimated using LSM, standard errors, 95% CIs, and nominal *P* values. Effect size was determined using Cohen *d* calculations based on the LSM estimates.

RESULTS

Patients

A total of 182 patients were randomized to KarXT or placebo; 83 patients in the KarXT group and 87 patients in the placebo group were included in the mITT analysis. Baseline characteristics for the study population have been reported[10] and are shown in Supplementary Table 3; they were similar between the 2 treatment groups and are fairly representative of demographics of other US-based inpatient studies for the treatment of schizophrenia.[22] Mean PANSS total scores at baseline were 97.3 ± 9.34 points in the KarXT group and 96.6 ± 8.39 points in the placebo group.

Categorical Response Rates

Figure 1 shows the responder rates for the KarXT and placebo groups at the week 5 study endpoint across all 4 PANSS response threshold categories. The proportion of KarXT patients meeting the categorical response rate criteria at the week 5 study endpoint ranged from 59.0% (n = 49) using the ≥ 20% threshold to 15.7% (n = 13) for the ≥ 50% threshold. Regardless of the response threshold evaluated, the proportion of KarXT patients responding was consistently higher than the proportion of placebo patients (nominal $P < .05$ for all response criteria). As the response threshold was increased, a smaller number of patients in both the KarXT and placebo groups met the response criteria, as expected. The corresponding NNTs (95% CI) for the number of patients needed to achieve a PANSS response at week 5 were NNT = 3 (3–5) for ≥ 20%, NNT = 4 (3–7) for ≥ 30%, NNT = 7 (4–20) for ≥ 40%, and NNT = 11 (6–145) for ≥ 50% improvement in PANSS total score between baseline and week 5.

Time Course of Response

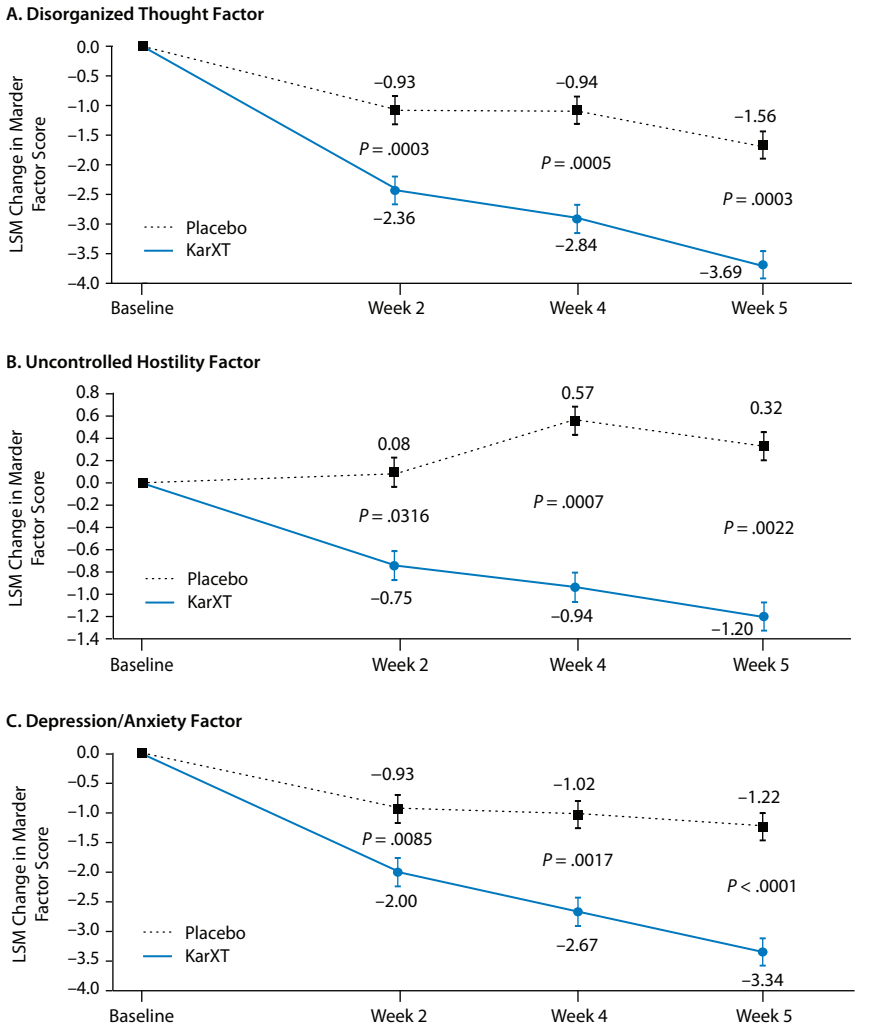
The time course for achievement of response based on each of the 4 response criteria is shown in Figure 2. Comparing the response of KarXT with that of the placebo group, the ≥ 20% and ≥ 30% threshold criteria showed significant differences favoring KarXT by week 2, whereas the ≥ 40% and ≥ 50% thresholds did not reach $P < .05$ until week 4.

Table 1. Positive and Negative Syndrome Scale: Marder 5-Factor Response by Treatment Assignment at Study Endpoint (Week 5)

Marder factor	Group	Baseline score, mean (SD)	Week 5 change from baseline, mean (95% CI)[a]	Week 5 KarXT – placebo, LSM difference (95% CI)	Cohen *d*
Positive symptom[b]	Placebo	30.6 (3.5)	−2.55 (−3.66 to −1.43)	−3.10 (−4.62 to −1.59)*	0.63
	KarXT	30.8 (3.8)	−5.65 (−6.82 to −4.48)		
Negative symptom[10,c]	Placebo	22.4 (5.1)	−1.32 (−2.29 to −0.35)	−2.53 (−3.85 to −1.22)**	0.59
	KarXT	22.3 (4.6)	−3.85 (−4.88 to −2.83)		
Disorganized thought[d]	Placebo	22.3 (4.1)	−1.56 (−2.39 to −0.73)	−2.13 (−3.27 to −1.00)***	0.58
	KarXT	22.1 (4.0)	−3.69 (−4.56 to −2.82)		
Uncontrolled hostility[e]	Placebo	9.5 (2.5)	0.32 (−0.39 to 1.03)	−1.52 (−2.49 to −0.56)****	0.48
	KarXT	9.7 (2.9)	−1.20 (−1.96 to −0.45)		
Anxiety/depression[f]	Placebo	11.9 (3.1)	−1.22 (−1.95 to −0.49)	−2.12 (−3.11 to −1.13)*	0.66
	KarXT	12.4 (2.8)	−3.34 (−4.11 to −2.57)		

[a]Represents within-group difference from baseline to week 5.
[b]Positive symptom factor includes 8 items; score range, 8–56.
[c]Negative symptom factor includes 7 items; score range, 7–49.
[d]Disorganized thought factor includes 7 items; score range, 7–49.
[e]Uncontrolled hostility factor includes 4 items; score range, 4–28.
[f]Anxiety/depression factor includes 4 items; score range, 4–28.
*P < .0001. **P = .0002. ***P = .0003. ****P = .0022.
Abbreviations: CI = confidence interval, LSM = least-squares mean, SD = standard deviation.

Figure 3. Effect of KarXT on the Symptom Domains of (A) Disorganized Thought, (B) Uncontrolled Hostility, and (C) Depression/Anxiety[a]



[a]Values are LSM change ± SE.
Abbreviation: LSM = least-squares mean.

Response on PANSS 5-Factor (Marder) Analysis

Patients in the KarXT group showed significant improvement over placebo from baseline to week 5 in all 5 PANSS Marder factors (Table 1). The effect size differences at week 5 ranged from 0.48 to 0.66. The between-group differences between KarXT and placebo were significant starting at week 2 for all 5 factors (Figure 3, Supplementary Figure 1).

DISCUSSION

The additional analysis presented here supports the primary and secondary endpoints of the recently published paper on the efficacy and safety of KarXT (xanomeline–trospium) in treating acute psychosis in patients with schizophrenia.[10] In summary, in this initial phase 2 study of KarXT for the treatment of patients with schizophrenia, KarXT showed a consistent pattern of statistical superiority compared with placebo on the likelihood of categorical treatment response, the time course of response, and all 5 PANSS factors.

As expected, the magnitude of response depended on the threshold criteria used. The lowest commonly accepted PANSS threshold for response is a 20% reduction of PANSS total symptoms.[14] Using these criteria, about 6 of 10 KarXT study patients met response criteria at week 5. Using the highest commonly accepted PANSS threshold of ≥ 50% reduction of symptoms,[14] about 1 of 7 patients receiving KarXT met response criteria at week 5. The NNT analysis provides a way to estimate the impact of KarXT treatment relative to placebo.[13] Lower NNTs denote more effective treatments. As expected, lower response thresholds resulted in lower NNTs, with the ≥ 20% threshold associated with the lowest NNT of 3, whereas the ≥ 50% threshold was associated with the highest NNT of 11. For the time course of improvement, clinically meaningful differences between KarXT and placebo were observed within 4 weeks for all 4 PANSS response criteria and within 2 weeks for 3 of the 4 PANSS response criteria in our analysis.

A 5-factor model of PANSS is now widely recognized as a more informative way to evaluate antipsychotic response to symptom domains than the original 3-subscale approach from the initial publication of PANSS,[23,24] which does not differentiate many of the clinically important domains, such as anxiety or depression, hostility, or cognitive symptoms. Most 5-factor models include these subdomains. The 5-factor analysis chosen here, known as Marder factors,[17,18,19] is widely used and reported in secondary analyses to provide response information on symptom subdomains.[19,25–27] Expanding the PANSS domains from 3 to 5 is helpful for understanding the pattern and types of symptom domains associated with KarXT treatment response. This may be of particular interest given KarXT's muscarinic receptor mechanism of action rather than direct dopamine receptor affinity, as with all currently marketed antipsychotic drugs.[4,5] Three of the 5-factor PANSS items were not reported in the primary and secondary analysis from this trial: disorganized thought, uncontrolled hostility, and anxiety/depression factors. The patterns of response to KarXT in all 3 of these factors were similar to those initially reported for the positive and negative symptom factors of the PANSS total. One caveat is that these 5 factors might not be independent of one another. In particular, for studies in acute schizophrenia, many PANSS items used across factors may be influenced by positive symptoms.[28] What might be scored as negative symptom items might be secondary to psychotic symptoms and will improve alongside positive symptoms. Therefore, the improvements observed in the 5-factor PANSS analysis are able to assess the more enduring and long-term nature of primary negative symptoms.

The main limitation of these results is that they are from a single, well-controlled phase 2 study and require replication. As the first efficacy study of a new investigational treatment for patients with schizophrenia, these findings should be considered preliminary. To confirm and extend these results, an active phase 3 program is underway, which includes 2 additional placebo-controlled trials of KarXT of similar design (EMERGENT-2, ClinicalTrials.gov identifier NCT04659161; EMERGENT-3, ClinicalTrials.gov identifier NCT04738123). As a single study, the results cannot be used to infer that KarXT is effective for schizophrenia, which needs to await completion of an ongoing phase 3 program. Furthermore, there was no active control arm, so the study cannot be used to compare KarXT with any other marketed or investigational antipsychotics. KarXT has not been studied in any head-to-head trials with other antipsychotic drugs; caution is needed when comparing the results of this trial to any other trial. As with all short-term trials, the 5-week duration limits the understanding of a longer-term response trajectory and durability of response, which will be addressed with data from longer-term follow-up studies included in the ongoing phase 3 studies of KarXT.

In summary, the analysis presented here shows that in this phase 2 trial, treatment with KarXT was associated with significant categorical responses over placebo across all PANSS threshold definitions evaluated, with demonstrated efficacy beginning as early as 2 weeks into treatment. Corresponding NNTs ranged from 3 for the lowest threshold definition of ≥ 20% reduction in total symptoms by 5 weeks to an NNT of 11 for the highest threshold of ≥ 50% reduction. Using a 5-factor PANSS analysis, KarXT improved all 5 factors at the first timepoint of assessment (2 weeks into treatment), showing that symptom improvements extend broadly beyond positive and negative symptoms and include cognitive, hostility, and affective domain symptoms, as well. If confirmed by the ongoing phase 3 studies, KarXT may represent a new class of antipsychotic drugs based on muscarinic receptor agonism.

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Supplementary Material

Article Title: 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

Authors: Peter J. Weiden, MD; Alan Breier, MD; Sarah Kavanagh, MPH; Andrew C. Miller, PhD; Stephen K. Brannan, MD; and Steven M. Paul, MD

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Supplementary Material

Supplementary Table 1. Original Positive and Negative Syndrome Scale (PANSS) Based on 3 Factors (Positive Symptoms, Negative Symptoms, General Symptoms)

Item Number (1-30)	Item Number (Positive, Negative, General)	Item Name	What It Measures
Original PANSS Positive Symptom Subscale			
1	P1	Delusion	Delusions
2	P2	Conceptual disorganization	Speech is confusing, hard to follow
3	P3	Hallucinatory behavior	Hallucinations
4	P4	Excitement	Over arousal, outbursts, hyperactivity
5	P5	Grandiosity	Unrealistic beliefs of superiority, abilities, fame, etc
6	P6	Suspiciousness/ persecution	Paranoid ideation and experience of persecution
7	P7	Hostility	Anger, resentment, up to assaultive behavior
Original PANSS Negative Symptom Subscale			
8	N1	Blunted affect	Reduced or absent facial expressions
9	N2	Emotional withdrawal	Lack of interest in life
10	N3	Poor rapport	In context, disengaged with interviewer
11	N4	Passive social withdrawal	Reduced or absent social functioning due to apathy and indifference to relationships
12	N5	Difficulty with abstract thinking	Concrete thinking (this is no longer considered a negative symptom; legacy item)
13	N6	Lack of spontaneity and flow of conversation	Conversation stilted, only minimal replies to questions
14	N7	Stereotyped thinking	Little thought content, repetitive or perseverative (also no longer considered a negative symptom)
Original PANSS General Symptom Subscale			
15	G1	Somatic concern	Worry about real or imagined health problems
16	G2	Anxiety	Subjective report of anxiety
17	G3	Guilt feelings	Self-blame, remorse may be accurate or delusional
18	G4	Tension	Physical manifestations of anxiety
19	G5	Mannerisms and posturing	Abnormal movements or postures
20	G6	Depression	Sadness, pessimism, etc
21	G7	Motor retardation	Reduction in general physical movements

22	G8	Uncooperativeness	Lack of cooperation, resentment, etc
23	G9	Unusual thought content	Bizarreness of delusions
24	G10	Disorientation	Unaware of surroundings
25	G11	Poor attention	Poor concentration, distractible
26	G12	Lack of judgment and insight	Not aware of condition or situation
27	G13	Disturbance of volition	Indecision, unable to start anything
28	G14	Poor impulse control	Inappropriate behaviors
29	G15	Preoccupation	Self-absorbed with internal experiences
30	G16	Active social avoidance	Differs from passive social withdrawal because this is caused by paranoia not apathy

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.

Supplementary Table 2. Positive and Negative Syndrome Scale (PANSS) 5 "Marder" Factors (Positive Symptoms, Negative Symptoms, Disorganized Thought, Hostility/Excitement, and Depression/Anxiety)

Original PANSS Item Number (1-30)	Original PANSS Item Number (Positive, Negative, General)	Item Name	What It Measures
Marder Positive Symptom Subscale (8 Items)			
1	P1	Delusion	Delusions
3	P3	Hallucinatory behavior	Hallucinations
5	P5	Grandiosity	Unrealistic beliefs of superiority, abilities, fame, etc
6	P6	Suspiciousness/ persecution	Paranoid ideation and experience of persecution
14	N7	Stereotyped thinking	Little thought content, repetitive or perseverative (no longer considered a negative symptom)
15	G1	Somatic concern	Worry about real or imagined health problems
23	G9	Unusual thought content	Bizarreness of delusions
28	G12	Lack of insight	No insight
Marder Negative Symptom Subscale (7 Items)			
8	N1	Blunted affect	Reduced or absent facial expressions
9	N2	Emotional withdrawal	Lack of interest in life
10	N3	Poor rapport	In context, disengaged with interviewer
11	N4	Passive social withdrawal	Reduced or absent social functioning due to apathy and indifference to relationships
13	N6	Lack of spontaneity and flow of conversation	Conversation stilted, only minimal replies to questions
21	G7	Motor retardation	Reduction in general physical movements
30	G16	Active social avoidance	Differs from passive social withdrawal because this is caused by paranoia not apathy
Marder Disorganized Thought (7 Items)			
2	P2	Conceptual disorganization	Speech is confusing, hard to follow
12	N5	Difficulty with abstract thinking	Concrete thinking (no longer considered a negative symptom; legacy item)

19	G5	Mannerisms and posturing	Abnormal movements or postures
24	G10	Disorientation	Unaware of surroundings
25	G11	Poor attention	Poor concentration, distractible
27	G13	Disturbance of volition	Indecision, unable to start anything
29	G15	Preoccupation	Self-absorbed with internal experiences
Marder Uncontrolled Hostility/Excitement (4 Items)			
4	P4	Excitement	Over arousal, outbursts, hyperactivity
7	P7	Hostility	Anger, resentment, up to assaultive behavior
22	G8	Uncooperativeness	Lack of cooperation, resentment, etc
28	G14	Poor impulse control	Inappropriate behaviors
Marder Depression/Anxiety (4 Items)			
16	G2	Anxiety	Subjective report of anxiety
17	G3	Guilt feelings	Self-blame, remorse may be accurate or delusional
18	G4	Tension	Physical manifestations of anxiety
20	G6	Depression	Sadness, pessimism, etc

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(12):538-546.

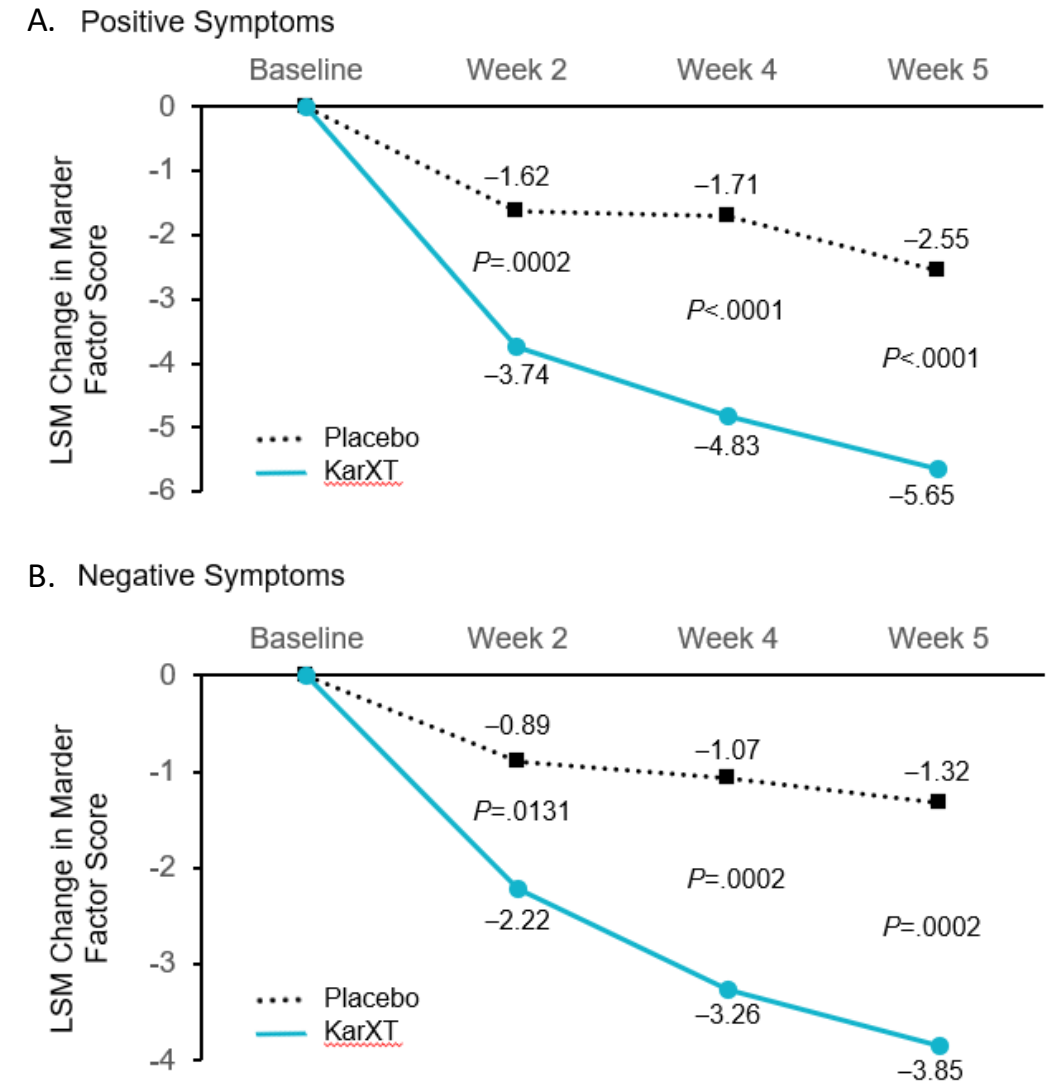
Supplementary Table 3. Patient Baseline Demographics[1]

Characteristic	KarXT (n=83)	Placebo (n=87)
Age (y), mean ± SD	43.7 ± 10.0	41.8 ± 10.0
Male sex, n (%)	67 (81)	64 (74)
PANSS total score, mean ± SD	97.3 ± 9.34	96.6 ± 8.39
PANSS Marder 5-factor baseline scores, mean ± SD		
Positive symptom factor	30.8 ± 3.8	30.6 ± 3.5
Negative symptom factor	22.3 ± 4.6	22.4 ± 5.1
Disorganized thought factor	22.1 ± 4.0	22.3 ± 4.1
Hostility/excitement factor	9.7 ± 2.9	9.5 ± 2.5
Depression/anxiety factor	12.4 ± 2.8	11.9 ± 3.1
CGI-S score, mean ± SD	5.0 ± 0.6	4.9 ± 0.6

Abbreviations: CGI-S=Clinical Global Improvement–Severity, PANSS=Positive and Negative Syndrome Scale, SD=standard deviation.

1. Brannan S, Breier A, Weiden PJ, Paul S, Miller A. The M1/M4 agonist xanomeline in combination with trospium is effective for acute treatment of schizophrenia: PANSS responder and PANSS 5-factor analyses of a phase 2 placebo-controlled inpatient trial. Presented at: Schizophrenia International Research Society Virtual Congress; pril 17-21, 2021.

Supplementary Figure 1. Effect of KarXT on the Symptom Domains of (A) Marder Positive Symptom factor and (B) Marder Negative Symptom factor*



Abbreviation: LSM=least squares means.

*Disorganized thought, uncontrolled hostility, and depression/anxiety factors are published in the manuscript (Figure 3).