SIRS S254

Open-Label, Randomized Study to Assess Safety and Efficacy of Slow and Accelerated Switching to Xanomeline/Trospium From Standard of Care Atypical Antipsychotics in Participants With Schizophrenia

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Background

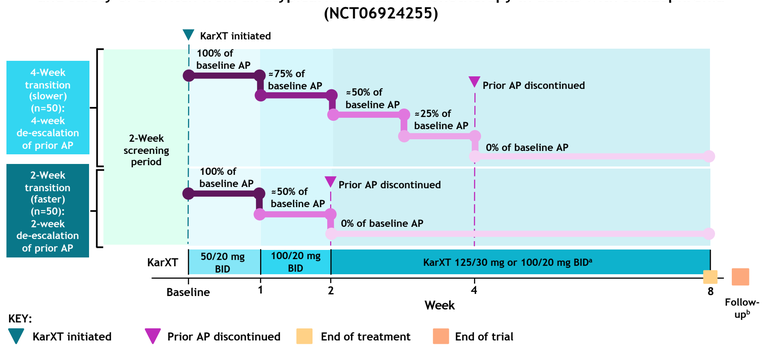
- Schizophrenia has historically been treated with antipsychotic (AP) medications; up until 2024, these have been primarily dopamine D_2 receptor antagonists[1]
- Traditional and atypical APs can cause significant side effects, including acute extrapyramidal adverse effects, tardive dyskinesia, neuroleptic malignant syndrome, and cardiometabolic adverse effects,[2,3] that are associated with high rates of treatment discontinuation and risk of relapse[4]
- Xanomeline/trospium chloride (KarXT) is a dual M_1/M_4 muscarinic receptor agonist combined with a peripheral pan muscarinic receptor antagonist that does not block D_2 dopamine receptors. The novel mechanism of action of KarXT has demonstrated a favorable side effect profile in adults with schizophrenia experiencing acute psychosis[5]
- Medication switching in individuals with schizophrenia is common, with reported rates of 30% within 1 year of initiation in clinical trials[6] and up to 50% within 6-24 months in real-world analyses[7]
- Despite the commonality of medication switching among individuals with schizophrenia, data and guidance on how to switch patients from an AP to a medication with a new mechanism of action are lacking

Objective

- The goal of this study was to examine 2 different methods of switching from oral atypical APs to KarXT monotherapy in clinically stable adults with schizophrenia

Methods

Study design of an 8-week, multicenter, randomized, open-label, outpatient trial assessing the efficacy and safety of a switch from an atypical AP to KarXT monotherapy in adults with schizophrenia (NCT06924255)



KarXT dose is expressed as xanomeline/trospium (mg/mg).
[a]Participants were initiated at KarXT 50 mg/20 mg BID for 1 week, uptitrated to KarXT 100 mg/20 mg for 1 week, and then uptitrated to a maintenance dose of KarXT 125 mg/30 mg BID based on tolerability and clinical response. Participants on KarXT 125 mg/30 mg twice daily may have down-tapered to 100 mg/20 mg as necessary based on their response. [b]A follow-up/end of trial visit was conducted at 7±2 days following the last dose of KarXT to evaluate safety and tolerability.
AP, antipsychotic; BID, twice daily, KarXT, xanomeline/trospium chloride.

- Participants in both treatment groups followed the same titration schedule, initiating KarXT at 50 mg/20 mg twice daily for 1 week, 100 mg/20 mg for 1 week, then uptitrating to a target maintenance dose of KarXT 125 mg/30 mg, if tolerated, over 8 weeks

Key inclusion and exclusion criteria

Key inclusion criteria
Males and females 18 to 65 years of age at screening
Primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 criteria and confirmed by the Mini-International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies (v7.0.2)
Taking an oral atypical AP medication at a stable dose and frequency for ≥6 weeks prior to screening
Psychiatrically stable (no psychiatric hospitalization, acute crisis intervention, or other increase in level of care due to symptom exacerbation within 12 weeks of screening)
Judged by the investigator to be an appropriate candidate for transitioning from the current oral AP therapy due to safety/tolerability concerns and/or insufficient efficacy
Body mass index ≥18 and ≤40 kg/m^2
PANSS total score ≤80 at screening and baseline
CGI-S score ≤4 at screening and at baseline
Key exclusion criteria
Any primary DSM-5 disorder, other than schizophrenia, within 6 months prior to screening, including bipolar-I or bipolar-II disorder, major depressive disorder, schizoaffective disorder, obsessive compulsive disorder, and posttraumatic stress disorder
History of schizophrenia treatment resistance, defined as a failure to respond to 2 courses of pharmacotherapy within the prior 12 months or a history of receipt of clozapine
Psychiatric hospitalization for >30 days within 12 months prior to screening
Clinically significant medical condition or history thereof that could jeopardize the safety of the participant or validity of the trial results
Current use of a long-acting injectable AP
Prior exposure to xanomeline or trospium chloride
Pregnant, breastfeeding, or <3 months postpartum

AP, antipsychotic; CGI-S, Clinical Global Impression-Severity; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; PANSS, Positive and Negative Syndrome Scale.

Objectives and endpoints

Primary objective Evaluate the all-cause KarXT discontinuation rate for faster and slower switching of atypical AP therapy to KarXT monotherapy over 8 weeks	**Primary endpoint** • All-cause KarXT discontinuation rate
Secondary efficacy objective Evaluate the effectiveness of switching outpatients from standard atypical AP therapy to KarXT monotherapy over 8 weeks	**Secondary efficacy endpoints** • KarXT discontinuations due to lack of efficacy • CfB to week 8 in PANSS total, CGI-S, and PSP scale scores
Secondary safety objective Evaluate the safety and tolerability of KarXT monotherapy following a switch from atypical APs	**Secondary safety endpoints** • KarXT discontinuations due to AEs • Incidence of AEs • CfB to week 8 in MSQ

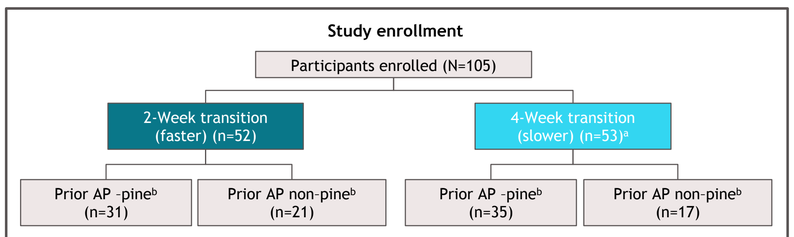
AE, adverse event; AP, antipsychotic; CfB, change from baseline; CGI-S, Clinical Global Impression-Severity; KarXT, xanomeline/trospium chloride; MSQ, Medication Satisfaction Questionnaire; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance.

Statistical analysis

- All analyses were descriptive in nature
- Data are summarized descriptively
- Least-squares (LS) mean differences were calculated via a mixed model for repeated measure analysis, including visit, visit by treatment interaction, and baseline score as covariates, with participants included as a repeated measure; the model was fit using an unstructured covariance matrix with the Kenward-Roger adjustment for the degrees of freedom

Results

Study enrollment



[a]AP type was not recorded in 1 participant in the slower transition group. [b]-pines=olanzapine and quetiapine; non-pines=aripiprazole, lurasidone, and risperidone.
AP, antipsychotic.

- 105 total participants were enrolled in the study with 63% (n=66) on a stable dose of a -pine AP (olanzapine or quetiapine) and 37% (n=38) on a non-pine AP (aripiprazole, lurasidone, or risperidone)

Duration of use and dose of prior AP medication

	Overall (N=105)	Total Population: 2-Week Transition (faster) (n=52)	Total Population: 4-Week Transition (slower) (n=53)
Duration of prior AP, mean (SD), months			
Aripiprazole (n=20)	28.1 (42.5)	42.2 (50.5)	6.87 (5.1)
Lurasidone (n=4)	43.5 (37.2)	14.0 (11.7)	73.1 (22.8)
Risperidone (n=14)	35.9 (32.2)	20.7 (16.4)	51.1 (37.9)
Olanzapine (n=36)	52.9 (70.1)	57.8 (76.2)	47.4 (64.5)
Quetiapine (n=30)	49.2 (58.9)	58.2 (51.7)	43.2 (63.9)
Dose of prior AP, mean (SD), mg			
Aripiprazole (n=20)	15.3 (4.7)	16.3 (5.3)	13.8 (3.5)
Lurasidone (n=4)	70.0 (34.6)	90.0 (42.4)	50.0 (14.1)
Risperidone (n=14)	4.0 (2.1)	3.8 (2.6)	4.1 (1.7)
Olanzapine (n=36)	15.4 (5.1)	15.8 (5.3)	15.0 (5.0)
Quetiapine (n=30)	338.3 (179.9)	300.0 (180.9)	363.9 (179.7)

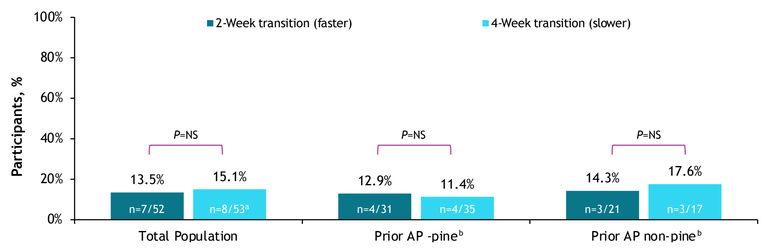
AP, antipsychotic; SD, standard deviation.

Baseline demographics and clinical characteristics

Characteristic	Overall (N=105)	Total Population: 2-Week Transition (faster) (n=52)	Total Population: 4-Week Transition (slower) (n=53)[b]	Prior AP -pine[a]: 2-Week Transition (faster) (n=31)	Prior AP -pine[a]: 4-Week Transition (slower) (n=35)	Prior AP non-pine[a]: 2-Week Transition (faster) (n=21)	Prior AP non-pine[a]: 4-Week Transition (slower) (n=17)
Age, mean (SD), years	46.2 (11.9)	47.2 (12.2)	45.2 (11.7)	48.1 (12.5)	45.5 (12.0)	45.8 (12.0)	45.7 (10.7)
Male, n (%)	78 (74.3)	36 (69.2)	42 (79.2)	22 (71.0)	27 (77.1)	14 (66.7)	14 (82.4)
Race, n (%)							
White	52 (49.5)	23 (44.2)	29 (54.7)	15 (48.4)	20 (57.1)	8 (38.1)	9 (52.9)
Black/African American	49 (46.7)	27 (51.9)	22 (41.5)	14 (45.2)	14 (40.0)	13 (61.9)	7 (41.2)
Multiple/ other	4 (3.8)	2 (3.8)	2 (3.8)	2 (6.5)	1 (2.9)	0	1 (5.9)
Ethnicity, n (%)							
Hispanic/ Latino	42 (40.0)	23 (44.2)	19 (35.8)	16 (51.6)	13 (37.1)	7 (33.3)	5 (29.4)
Non-Hispanic/ non-Latino	58 (55.2)	27 (51.9)	31 (58.5)	14 (45.2)	21 (60.0)	13 (61.9)	10 (58.8)
Not reported/ unknown	5 (4.8)	3 (5.7)	5 (4.8)	1 (3.2)	1 (2.9)	1 (4.8)	2 (11.8)
Weight, mean (SD), kg	86.8 (16.9)	88.3 (15.9)	85.3 (17.8)	90.5 (17.9)	83.9 (17.8)	85.8 (13.7)	87.0 (18.9)

[a]-pines=olanzapine and quetiapine; non-pines=aripiprazole, lurasidone, and risperidone. [b]AP type was not recorded in 1 participant in the slower transition group.
AP, antipsychotic; SD, standard deviation.

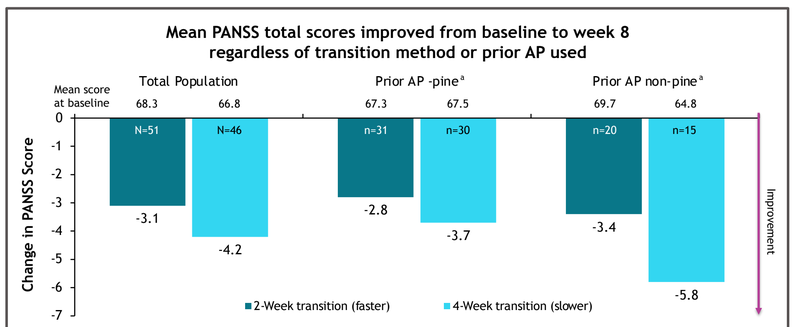
All-cause discontinuation of KarXT over 8 Weeks



[a]AP type was not recorded in 1 participant in the slower transition group who discontinued. [b]-pines=olanzapine and quetiapine; non-pines=aripiprazole, lurasidone, risperidone.
AP, antipsychotic; KarXT, xanomeline/trospium chloride; NS, not significant.

- Most participants (86%) completed 8 weeks of treatment
  - 15 participants (14.3%) discontinued KarXT early
- There were no discontinuations because of lack of efficacy

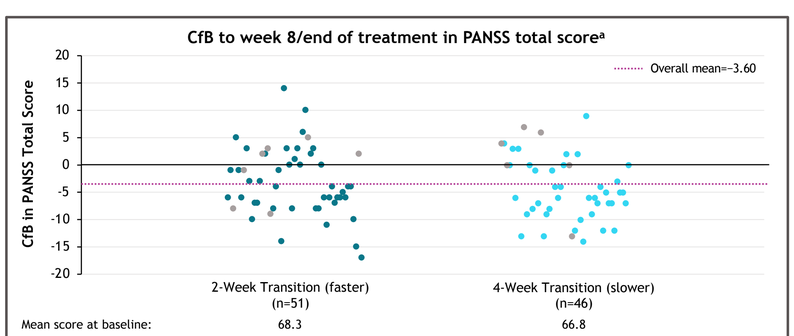
Mean PANSS total scores improved from baseline to week 8 regardless of transition method or prior AP used



[a]-pines=olanzapine and quetiapine; non-pines=aripiprazole, lurasidone, and risperidone.
AP, antipsychotic; PANSS, Positive and Negative Syndrome Scale.

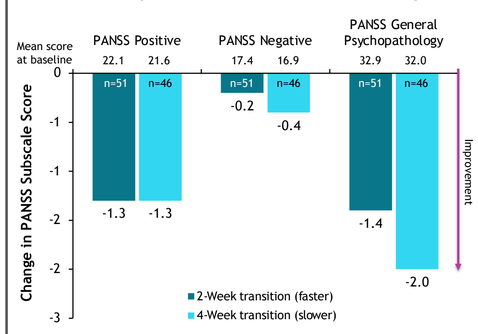
- The mean Positive and Negative Syndrome Scale (PANSS) score change from baseline (CfB) to week 8 was -3.6 (standard error [SE]: 0.6): -3.1 (LS mean [SE]: -3.1 [0.8]) in the 2-week transition (faster) group, and -4.2 (LS mean [SE]: -4.1 [0.9]) in the 4-week transition (slower) group (LS mean difference: 1.0; *P*=0.4000)

CfB to week 8/end of treatment in PANSS total score[a]



[a]Colored dots represent change at week 8. Gray dots represent change at end of treatment/prior to week 8. A total of 8 patients are not included because they did not have PANSS evaluation at end of treatment.
CfB, change from baseline; PANSS, Positive and Negative Syndrome Scale.

Mean PANSS positive, negative, and general psychopathology subscale scores improved from baseline to week 8 regardless of the transition method



CfB	2-Week Transition (faster)	4-Week Transition (slower)
PANSS positive		
LS mean (SE)	−1.4 (0.3)	−1.2 (0.3)
LS mean difference	-0.2	
P value	0.5882	
PANSS negative		
LS mean (SE)	−0.1 (0.3)	−0.5 (0.3)
LS mean difference	0.4	
P value	0.4190	
PANSS general psychopathology		
LS mean (SE)	−1.4 (0.6)	−2.1 (0.6)
LS mean difference	0.7	
P value	0.4259	

CfB, change from baseline; LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

Other secondary endpoints

- Mean Clinical Global Impression-Severity (CGI-S) scores improved from baseline to week 8 regardless of the transition method or prior AP used
  - Total population: 2-week transition, CfB=−0.2; 4-week transition, CfB=−0.2
  - Prior AP -pine: 2-week transition, CfB=−0.1; 4-week transition, CfB=−0.2
  - Prior AP non-pine: 2-week transition, CfB=−0.3; 4-week transition, CfB=−0.3
- Mean CfB to week 8 in Personal and Social Performance (PSP) scale scores improved overall regardless of the transition method
  - Total population: 2-week transition, CfB=0.7; 4-week transition, CfB=1.1
  - Prior AP -pine: 2-week transition, CfB=0.0; 4-week transition, CfB=1.3
  - Prior AP non-pine: 2-week transition, CfB=2.0; 4-week transition, CfB=1.0
- Mean CfB to week 8 in Medication Satisfaction Questionnaire (MSQ) scores improved overall in both the faster and slower transition groups
  - Total population: 2-week transition, CfB=0.4; 4-week transition, CfB=0.1
  - Prior AP -pine: 2-week transition, CfB=0.1; 4-week transition, CfB=0.3
  - Prior AP non-pine: 2-week transition, CfB=0.8; 4-week transition, CfB=-0.2

Summary of treatment-emergent adverse events

	Overall (N=105)	Total Population: 2-Week Transition (faster) (n=52)	Total Population: 4-Week Transition (slower) (n=53)	Prior AP -pine[a]: 2-Week Transition (faster) (n=31)	Prior AP -pine[a]: 4-Week Transition (slower) (n=35)	Prior AP non-pine[a]: 2-Week Transition (faster) (n=21)	Prior AP non-pine[a]: 4-Week Transition (slower) (n=17)
Participants with ≥1 TEAE	51 (48.6)	26 (50.0)	25 (47.2)	14 (45.2)	19 (54.3)	12 (57.1)	6 (35.3)
TEAEs by severity							
Mild	41 (39.0)	19 (36.5)	22 (41.5)	8 (25.8)	17 (48.6)	11 (52.4)	5 (29.4)
Moderate	10 (9.5)	7 (13.5)	3 (5.7)	6 (19.4)	2 (5.7)	1 (4.8)	1 (5.9)
Severe	0	0	0	0	0	0	0
≥1 TEAE leading to study drug discontinuation	3 (2.9)	2 (3.8)	1 (1.9)	2 (6.5)	1 (2.9)	0	0
≥1 TEAE leading to study discontinuation	2 (1.9)	2 (3.8)	0	2 (6.5)	0	0	0
≥1 serious TEAE	0	0	0	0	0	0	0

[a]-pines=olanzapine and quetiapine; non-pines=aripiprazole, lurasidone, risperidone.
AP, antipsychotic; TEAE, treatment-emergent adverse event.

- Approximately 50% of all participants had ≥1 treatment-emergent adverse event (TEAE)
- No TEAEs were serious
- 2.9% of participants discontinued KarXT early due to a TEAE
- Rates of TEAEs were consistent with those reported in pooled analyses of the EMERGENT-1, EMERGENT-2, and EMERGENT-3 trials[1]

Select treatment-emergent adverse events

Treatment-emergent adverse event, n (%)	Overall (N=105)	Total Population: 2-Week Transition (faster) (n=52)	Total Population: 4-Week Transition (slower) (n=53)	Prior AP -pine[c]: 2-Week Transition (faster) (n=31)	Prior AP -pine[c]: 4-Week Transition (slower) (n=35)	Prior AP non-pine[c]: 2-Week Transition (faster) (n=21)	Prior AP non-pine[c]: 4-Week Transition (slower) (n=17)
Procholinergic							
Nausea[a]	14 (13.3)	10 (19.2)	4 (7.5)	5 (16.1)	2 (5.7)	5 (23.8)	2 (11.8)
Vomiting[b]	12 (11.4)	6 (11.5)	6 (11.3)	4 (12.9)	5 (14.2)	2 (9.5)	1 (5.9)
Diarrhea	4 (3.8)	3 (5.8)	1 (1.9)	2 (6.5)	1 (2.9)	1 (4.8)	0
Anticholinergic							
Constipation	7 (6.7)	4 (7.7)	3 (5.7)	4 (12.9)	2 (5.7)	0	1 (5.9)
Dry mouth	9 (8.6)	3 (5.8)	6 (11.3)	3 (9.7)	5 (14.3)	0	1 (5.9)
Drowsiness	5 (4.8)	2 (3.8)	3 (5.7)	2 (6.5)	2 (5.7)	0	1 (5.9)
Other							
Headache	4 (3.8)	2 (3.8)	2 (3.8)	2 (6.5)	1 (2.9)	0	1 (5.9)
Weight gain	3 (2.9)	1 (1.9)	2 (3.8)	0	1 (2.9)	1 (4.8)	1 (5.9)

[a]Includes verbatim terms nausea, intermittent nausea, and nausea/vomiting. [b]Includes verbatim terms vomiting, emesis, and nausea/vomiting.
[c]-pines=olanzapine and quetiapine; non-pines=aripiprazole, lurasidone, and risperidone.
AP, antipsychotic.

- Most common TEAEs were largely anticholinergic and procholinergic and included nausea, vomiting, dry mouth, and constipation
  - Overall, 9.5% (n=10) of participants used medications to alleviate nausea/vomiting (ie, calcium carbonate [n=8], ondansetron [n=2]); 9.6% (n=5) and 9.4% (n=5) of participants in the 2-week (faster) and 4-week (slower) transition groups, respectively, used anti-nausea medications
- No participants discontinued due to worsening psychosis
- Mean (standard deviation [SD]) change in weight from baseline to week 8 was -0.3 (3.4) kg among the 2-week (faster) transition group (prior -pine AP, -0.8 [3.4] kg; prior non-pine AP, 0.4 [3.5] kg) and -0.1 (2.7) kg among the 4-week (slower) transition group (prior -pine AP, 0.2 [2.8] kg; prior non-pine AP, -0.7 [2.6] kg)

Conclusions

- Overall, both the 2-week (faster) and 4-week (slower) transitions from oral atypical APs to KarXT were generally safe and maintained clinical stability among adults with schizophrenia, suggesting that either transition method may be considered
- In a subanalysis of prior AP, there were no significant differences in rates of discontinuations between the 2-week and 4-week transitions of -pine/non-pine APs
- These results may aid clinical decision-making, providing healthcare providers with evidence-based guidance on how to switch to KarXT from current atypical APs

Reference

1. McCutcheon RA, et al. *Lancet Psychiatry*. 2025;12:384-394. 2. Trollor JN, et al. *CNS Drugs*. 2009;23:477-492. 3. Huhn M, et al. *Lancet*. 2019;394:939-951. 4. Kishi T, et al. *Psychol Med*. 2019;49:772-779. 5. Kaul I, et al. *J Clin Psychiatry*. 2025;86:24m15497. 6. Nyhuis AW, et al. *BMC Psychiatry*. 2010;10:75. 7. Martin A, et al. *Adv Ther*. 2022;39:3933-3956.

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