Characterizing the Antipsychotic Activity and Safety Profile of the Novel Muscarinic Agonist KarXT (Xanomeline + Trospium): Primary and Secondary Results from a Phase 2 Placebo-Controlled Trial in Schizophrenia

Colin Sauder, PhD; Peter Weiden, MD; Stephen Brannan, MD; Sharon Sawchak, RN; Sarah Kavanagh, MPH; Andrew Miller, PhD; Alan Breier, MD; Steven Paul, MD

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BACKGROUND

KarXT is an investigational antipsychotic that preferentially activates CNS M_1 and M_4 muscarinic receptors and does not directly bind to D_2 receptors

KarXT is a combination of xanomeline, a centrally active muscarinic receptor agonist, and trospium, an FDA-approved peripheral anti-cholinergic drug that does not measurably cross the blood-brain barrier

A Phase 2 trial in adults with schizophrenia experiencing psychotic symptom exacerbation **(EMERGENT-1; NCT03697252)** has been completed with the primary and secondary efficacy and safety results recently published[4]

- KarXT showed a reduction in symptoms of schizophrenia across the primary endpoint (Figure 1) and key secondary endpoints[4]
- Favorable safety and tolerability profile (Table 2), including no clinically meaningful weight gain or EPS (Table 4)

Additional EMERGENT-1 analyses presented here provide further insight into the antipsychotic activity of KarXT and underscore the potentially unique safety and tolerability profile of this compound.

METHODS

Trial Overview:

Randomized, double-blind, placebo-controlled, 5-week, multi-site, in-patient trial in patients with schizophrenia experiencing an acute symptom exacerbation

182 participants; any previous antipsychotics washed out prior to 1:1 randomization to KarXT or placebo

KarXT flexibly dosed at either 100mg/20mg or 125mg/30mg of xanomeline/trospium BID based on tolerability

Outcome Measures:

Pre-specified efficacy analyses (week 5, KarXT vs. placebo):

- Least-squares mean (LSM) change from baseline in PANSS-total, PANSS-positive, PANSS-negative, PANSS Marder negative
- CGI-S score frequency counts, percentage of patients with CGI-S score 1 or 2

Post hoc efficacy analyses
(responders per study week, KarXT vs. placebo):

- ≥ 30% reduction from baseline in PANSS total score, scale: 0-6 (0-180 range)
- ≥ 2 point reduction from baseline in CGI-S

Safety and tolerability:

- Adverse events (AE) rates and duration, laboratory findings, EPS rating scales

Analyses:

All efficacy analyses employed the modified intent-to-treat (mITT) population, defined as all randomized participants who received at least one dose of study medication and had a baseline and at least one post-baseline PANSS-Total assessment (KarXT: n = 83; pbo: n = 87)

Treatment effects for pre-specified analyses presented here were calculated using a mixed-effects model for repeated measures (MMRM) with no imputation for missing data

Treatment effects for *post hoc* analyses presented here were calculated using a logistic regression model with missing data imputed using last observation carried forward (LOCF) methodology

All safety and tolerability analyses employed descriptive statistics in the safety population, defined as all participants who received at least one dose of study medication (KarXT: n = 89; pbo: n = 90)

RESULTS

Key baseline demographics and symptom scores

Table 1 – Key Demographics and Baseline Characteristics (mITT population)*

	KarXT (n = 83)	Placebo (n = 87)
Mean age (years) ± SD	43.7 ± 10.0	41.8 ± 10.0
Gender, male (%)	80.7	73.6
Race (% non-white)	77.1	80.4
Mean Baseline PANSS Total Score ± SD	97.3 ± 9.3	96.6 ± 8.4
Mean Baseline CGI-S Score	5.0 ± 0.5	4.9 ± 0.6

*Plus-minus values are mean ± SD

Pre-specified primary endpoints and key secondary efficacy endpoints

KarXT treatment was associated with statistically significant reductions in PANSS-Total score compared with placebo at week 5:

- PANSS-Total primary endpoint (11.6-point treatment difference in least-squares mean change from baseline, p < 0.0001; Cohen's d = 0.75)

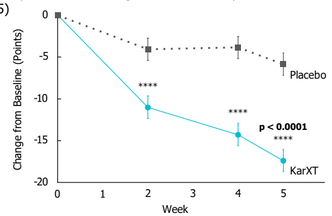


Fig. 1 – At week 5, the LSM change from baseline on PANSS-Total score in the KarXT arm compared to the placebo arm was -17.4 vs. -5.9 points; ****p < 0.0001.

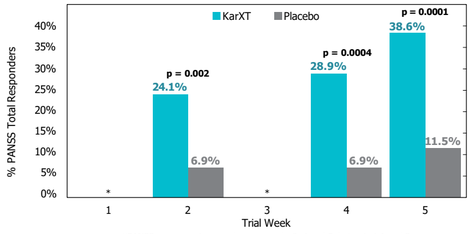
- Four out five pre-specified secondary outcome measures: PANSS-positive subscore, PANSS-negative subscore, and PANSS Marder negative factor and CGI-S frequency counts (all p < 0.001).[4] The percentage of participants who achieved a CGI-S score of 1 or 2 was not statistically different between treatment arms (p = 0.151).

Post hoc efficacy analyses: PANSS-Total and CGI-S responses as a function of trial week

PANSS-Total categorical response: ≥ 30% improvement

Significant treatment effect for KarXT vs. placebo at every assessed time point, beginning at two weeks; response was measured as percentage of participants who achieved a ≥ 30% improvement from baseline in PANSS-Total score

At endpoint (week 5), 38.6% of participants in the KarXT arm were responders, compared to 11.5% of participants in the placebo arm (OR = 4.83, 95% CI = 2.2-10.7, p = 0.0001), number needed to treat = 4



*PANSS assessments were done on weeks 2, 4 and 5, but not at 1 and 3

Fig. 2 – Percentage of participants who achieved ≥ 30% improvement from baseline in PANSS-Total score as a function of study week.

CGI-S response: ≥ 2-point improvement

Treatment effect favors KarXT vs. placebo at every assessed time point, with statistical significance reached at week 4 and sustained through week 5

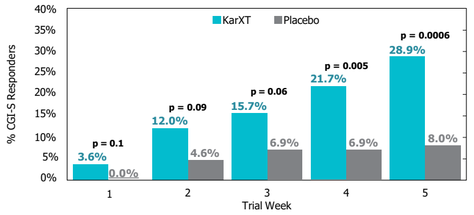


Fig. 3 – Percentage of participants who achieved ≥ 2-point improvement from baseline in CGI-S score as a function of study week.

Safety and tolerability overview

Overall rates of treatment emergent AEs (TEAEs) similar in KarXT and placebo arms (54% vs. 43%); TEAE-related discontinuations similar in KarXT and placebo arms (n = 2 per arm)

The majority of the most common (>5% in the KarXT arm) TEAEs were pro-cholinergic or anti-cholinergic

91% of participants in the KarXT arm titrated to highest dose (vs. 97% on placebo); 4% titrated back down (vs. 1% on placebo)

Table 2 – Most Common AEs – Number (Percent) of Participants

Treatment-Emergent AEs > 5% in KarXT arm	KarXT (n = 89)	Placebo (n = 90)
Constipation	15 (16.9%)	3 (3.3%)
Nausea	15 (16.9%)	4 (4.4%)
Dry mouth	8 (9.0%)	1 (1.1%)
Dyspepsia	8 (9.0%)	4 (4.4%)
Vomiting	8 (9.0%)	4 (4.4%)
Headache	6 (6.7%)	5 (5.6%)
Somnolence	5 (5.6%)	4 (4.4%)

All AEs that occurred at > 5% in the KarXT arm were rated mild or moderate in severity; not associated treatment discontinuations

Table 3 – Severity of Key Pro-cholinergic and Anti-cholinergic AEs – Number (Percent) of Total Events

	KarXT		Placebo	
	Mild	Moderate	Mild	Moderate
Constipation	12/16 (75.0%)	4/16 (25.0%)	2/3 (67.7%)	1/3 (33.3%)
Nausea	13/15 (86.7%)	2/15 (13.3%)	3/4 (75.0%)	1/4 (25.0%)
Dry mouth	6/8 (75.0%)	2/8 (25.0%)	1/1 (100%)	0/1 (0.0%)
Vomiting	5/8 (62.5%)	3/8 (37.5%)	3/4 (75.0%)	1/4 (25.0%)

Duration of key pro-cholinergic and anti-cholinergic AEs

Majority of pro-cholinergic AEs in the KarXT arm were transient in nature, lasting ≤ 1 day for vomiting and ≤ 9 days for nausea

Majority of anti-cholinergic AEs (dry mouth; constipation) in the KarXT arm lasted < 2 weeks

Non-normal duration distributions of nausea and constipation duration, with broad range for both KarXT and placebo

Overall, AE duration appeared similar in KarXT and placebo arms

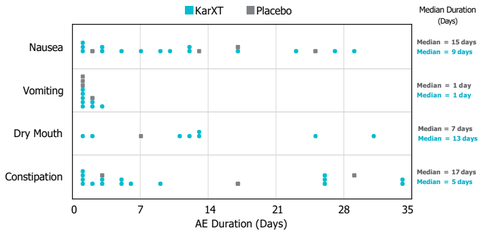


Fig. 4 – Individual event duration for key pro-cholinergic (nausea, vomiting) and anti-cholinergic (dry mouth, vomiting) AEs. Duration was calculated as (AE end date-AE start date) +1, except for two instances that were ongoing at the end of the trial, wherein duration was imputed using each participant's end of study date instead of AE end date.

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Table 4 – Additional Safety Data

Variable	KarXT (n = 89)	Placebo (n = 90)
Extrapyramidal symptoms (EPS)		
Akathisia AE reported – no. (%)	3 (3.4%)	0 (0%)
Mean change from baseline in SAS score at wk 5	−0.1 ± 0.7	−0.1 ± 0.8
Mean change from baseline in BARS score at wk 5	−0.1 ± 1.0	0.0 ± 0.7
Weight-related observations		
Greater than 7% increase in weight at wk 5 – no. (%)	2 (2.2%)	5 (5.6%)
Mean change in body weight from baseline to wk 5 – kg	1.5 ± 2.8	1.1 ± 3.5
Liver function tests*		
ALT > 3X ULN – no. (%)	0 (0%)	1 (1.1%)
AST > 3X ULN – no. (%)	0 (0%)	1 (1.1%)
GGT > 2X ULN – no. (%)	2 (2.2%)	1 (1.1%)
Cardiac		
Mean change in QTcF from baseline to wk 5 – msec	-2.7 ± 22.0	-3.8 ± 17.5
Mean change in orthostatic blood pressure baseline to wk 5		
Systolic – mmHg	-0.4 ± 11.9	-1.0 ± 11.3
Diastolic – mmHg	-0.9 ± 7.8	-1.3 ± 10.4

*There were no clinically significant elevations in alkaline phosphatase or total bilirubin reported. Plus-minus values are mean ± SD. SAS = Simpson Agnus Scale; BARS = Barnes Akathisia Rating Scale; ULN = upper limit of normal.

KarXT was not associated with increased EPS symptoms on the SAS or BARS compared to placebo. In the KarXT arm, 3 subjects reported symptoms that were classified as akathisia by site investigators during the trial; all of these symptoms resolved during the trial without changes in the dose.

Compared to placebo, KarXT was not associated with weight gain, change in orthostatic blood pressure, or corrected QT interval elongation.

Two subjects on KarXT experienced elevations in GGT > 2x ULN. A single subject on placebo reported elevated ALT, AST, and GGT. No subjects met criteria for potential drug induced liver injury.

CONCLUSIONS

Post hoc analyses of EMERGENT-1 data:

Provide additional support for and insight into the clinical meaning of the robust antipsychotic activity seen in primary analyses of KarXT in acutely psychotic patients with schizophrenia

Differential efficacy of KarXT in both PANSS-T and CGI-S responder analyses; rapid separation from placebo and significant treatment difference reached before endpoint

Emphasize KarXT tolerability in patients with schizophrenia

Most common AEs were pro-cholinergic and anti-cholinergic in nature; all were mild-to-moderate in severity and not associated with treatment discontinuation

The majority of key pro-cholinergic and anti-cholinergic AEs were transitory and lasted < 2 weeks (most vomiting lasted ≤ 1 day)

KarXT was not associated with many of the most common AEs associated with current antipsychotics such as somnolence, weight gain, or EPS

There was no evidence of drug induced liver injury, orthostatic hypotension, or syncope

Based on these results for the treatment of adults with schizophrenia, KarXT entered Phase 3 trials in December 2020